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CONTENTS

	Page
Tuberculosis of the Pericardium; A Study of Twenty Cases. Chester S. Keefer	1085
Fulminating Septicemia Associated with Purpura and Bilateral Adrenal Hemorrhage (Waterhouse-Friderichsen Syndrome); Report of Two Cases with Review of the Literature. Milton S. Sacks	1105
Variations in Response to Therapy in Pernicious Anemia. L. Mary Moench	1115
Arachnodactyly and Status Dysraphicus; A Review. Ralph H. Pino, Edmond L. Cooper, and Stefan Van Wien	1130
Clinical Manifestations and Studies in Parenchymatous Hepatitis. Hugo A. Freund	1144
Pain and Pain Equivalents in Heart Disease. Clough Turrill Burnett	1156
Angina Pectoris and Pernicious Anemia (Old Terminology), A Résumé of the Literature, with a Case Report. Hugh Stalker	1172
Bodily Build and Heredity in Coronary Thrombosis. Grace A. Goldsmith and Fredrick A. Willius	1181
The Effectiveness of Trichlorethylene in Preventing Attacks of Angina Pectoris. William S. Love, Jr.	1187
Case Reports:	
Treatment of Hemolytic Streptococcic Meningitis with Para-Amino-Benzene-Sulfonamide; Report of a Case, with Recovery. James G. Arnold, Jr.	1198
Intermittent Hyperthermia of Seven Years' Duration. Edgar V. Allen	1204
Primary Carcinoma of the Liver with Bone Metastasis. Herman Bolker, Mendel Jacobi, and Morris T. Koven	1212
Electrocardiographic Changes with Perforated Duodenal Ulcer; A Case Report. Lemuel C. McGee, Harold A. Conrad, and Angus K. Wilson	1222
Editorial	1227
Reviews	1230
College News Notes	1233

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TWENTY-FIRST ANNUAL SESSION

of the

AMERICAN COLLEGE OF PHYSICIANS

St. Louis, Mo., April 19–23, 1937

HEADQUARTERS: New Jefferson Hotel

A POSTGRADUATE WEEK DEVOTED TO INTERNAL MEDICINE AND ALLIED SPECIALTIES, led by eminent authorities. The Program consists of formal addresses, practical lectures, roundtable discussions, demonstrations, clinics and ward walks, arranged through the cooperation of St. Louis institutions.

The Program will be published in the March issue of this journal.

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ANNALS OF
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TUBERCULOSIS OF THE PERICARDIUM; A STUDY OF TWENTY CASES *

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TUBERCULOSIS of the pericardium is the least common and most serious tuberculous infection of the serous membranes. Generally speaking, it is infrequent, and since it has various clinical features which may not direct one's immediate attention to the pericardium, I am reviewing a series of 20 cases which were observed over a period of several years. The details of the cases are indicated in table 1.

ANALYSIS OF CASES

Age. It is agreed that tuberculosis of the pleurae and peritoneum is most often seen between the ages of 15 and 40 years. Everyone who has studied tuberculosis of the pericardium remarks that it is found most frequently over 40 years of age.[1, 2] This group of cases was no exception to that statement. Table 2 illustrates this very well. There were 17 men and three women.

Duration of Disease. Of this group, 18 died and two survived. There were 17 necropsies in the fatal cases. Of those who died, it was sometimes difficult to determine the exact duration of the disease, but it was commonly found to be one month to one year after the onset of symptoms, the average duration being from two to four months.

Pathology. In seven of the 20 cases there were signs of a large collection of fluid in the pericardium. In the others, the exudate was fibrinous and frequently measured 1 to 3.5 centimeters in thickness. In one there was calcification. Eleven of the cases showed enlargement and tuberculosis of the mediastinal lymph nodes. There was an associated tuberculosis of the lungs in three cases, of the pleura in seven cases, and of the peritoneum and epididymis, each in one. Four of the patients finally died of miliary

* Read before the Annual Meeting of the American Climatological and Clinical Association, Richmond, Virginia, October 27, 1936.

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TABLE I

Summary of Twenty Cases of Tuberculosis of the Pericardium

Case Number	Symptoms	Physical Signs							Fever	W.B.C.	Duration of Illness	Anatomical	Remarks
		Size of Heart (cm.)	Friction Rub	Pericardial Fluid	Murmurs	Arrhythmias	B.P. Systolic/ Diastolic	Edema					
Wasting Disease with Obscure Fever													
1. 70 ♂	Progressive weakness 2 mos. Loss of weight. Constriction across chest 6 wks.	10×7	+	0	0 Feeble breath sounds	0	144/66	0	100°–103°	5,900	3 mos.	Tbc. lymph nodes. Tbc. pericarditis	
2. 72 ♂	Loss of weight; weakness; fever; mental confusion	12×3	0	0	0	0	130/88	0	99°–100.4°	16,500	?	Tbc. pericarditis. Tbc. lymphadenitis of the tracheobronchial lymph nodes. Chronic tbc. with cavity	
3. 71 ♂	Loss of weight; weakness; fever	12×3	0	0	0	0	?	0	Normal 101°–102.8°	18,000–20,000	? 4½ wks. on ward		
4. 60 ♀	Fever; loss of weight and weakness	13×3	0	0	0		111/78	0	100°–102°	19,600	?	Tbc. epididymis. Miliary tbc. Obliterative fibrous pericarditis with calcification	Miliary tbc.
Heart Failure with Congestion													
5. 63 ♂	Dyspnea 10 mos. Edema of legs 5 mos.	11.5×3	0	0	0 Sounds distant	0	90/30	+ Generalized	0	8,200	10 mos.	Adherent pericardium. Tbc. pericarditis. Rt. hydrothorax. Miliary tbc. of lungs. Ascites. C.P.C. of liver and viscera	Progressive heart failure. Terminal miliary tbc.; afebrile; cyanosis striking
6. 60 ♂	Constriction in chest 2 mos. Shortness of breath 2 mos. Edema of legs 6 wks.	12×4	0	0	0 Sounds distant	0	135/90	+ Generalized	0	11,000	2 mos.	Tbc. bronchial and mediastinal lymph nodes. Tbc. pericarditis and pleurisy. Hypertrophy of heart. Hydrothorax. Ascites	Progressive heart failure, onset suggesting pericardial or coronary artery disease
7. 22 ♂	Pain in chest and abdomen 1 mo. Cough 1 mo. Abnormal swelling 3 wks.	14×5	0	0	0	0	115/70	0	99°–103°	12,000	2 mos.	Tbc bronchial and mediastinal lymph nodes. Tbc. pericarditis. Dilatation of heart. C.P.C. of viscera	Great cardiac enlargement. Pericardium varied from 2.5 to 3.5 cm. in thickness at necropsy. Miliary tbc.
8. 26 ♂	Pain in chest and abdomen 5 mos. Shortness of breath 3 mos. Edema 1 mo. Precordial pain 1 mo.	12×4	0	0	0	0	110/60	+ Generalized	97°–100.4°	10,000	5 mos.	Tbc. pericarditis. Tbc. bronchial lymph nodes. Miliary tbc. of lungs, pleura, spleen, liver. Ascites and bilateral hydrothorax	Febrile illness at onset followed by heart failure within 3 months
9. 43 ♂	Pain in chest. Dyspnea; cough; swelling of abdomen and feet	12×3	0	0	0 Sounds distant	0	110/80	+ Dependent	99°–102°	4,250	2½ mos.	Tbc. of bronchial and mediastinal lymph nodes. Tbc. pericarditis. C.P.C. of viscera	

TABLE I—*Continued*

Heart Failure with Congestion—*Continued*

43 ♂	cough; swelling of abdomen and feet				Sounds distant			Dependent				C.P.C. of viscera	

TABLE I—*Continued*

Heart Failure with Congestion—*Continued*

10. 81 ♂	Failing health for 1 yr. Dyspnea and constriction across chest 2 mos. Cough 2 mos.	11×4	+ 2 wks.	0	0 Faint heart sounds	Auricular fibrillation	105/75	+	99°–101°	7,400–14,000	1 yr.	Tuberculous pericarditis. Tbc. of pleura—bilateral. Tbc. tracheobronchial nodes	
11. 50 ♂	Pain in epigastrium and upper part of left scapular region 2 mos. Dyspnea 2 wks. Edema 2 wks.	12×4	0	0 700 c.c.	0	Auricular tachycardia with partial heart block and dropped beats	134/110	Dependent	0	5,200	2 mos.	Tbc. pericarditis. Obstructive pleuritis. Left hydrothorax. Tbc. of bronchial and mediastinal nodes	
12. 74 ♂	General malaise for 3 mos. Edema of extremities 2 mos. Dyspnea on exertion. Orthopnea	13×4	0	+	Faint heart sounds	Sino-auricular tachycardia. Left ventricular preponderance	110/95	+ Dependent ascites	98.6°–101°	4,500	5 mos.	Tbc. pericarditis with effusion (300 c.c.). Coronary arteriosclerosis. C.P.C. of viscera	Miliary tbc.
Pericardial Effusion													
13. 24 ♀	Pain in chest 1 mo.	13.5×4	+	+	0 Faint heart sounds	0	105/75	0	99°–101°	4,200	6 mos.		Recovered
14. 49 ♂	Pain and constriction in chest 1 mo. Dyspnea 1 mo. Loss of weight	15×7	0	+ Tapped twice	Soft systolic at apex	0	126/87	0 Liver enlarged	99°–101°	12,600	1 mo.	Pericarditis with effusion. Tbc. of mediastinal lymph nodes. Pleurisy with effusion	Pericardial cavity contained 3500 c.c. at necropsy
15. 70 ♂	Pain in left chest 2 wks. Dyspnea 2 wks. Edema of legs 2 wks.	13×4	+	+ Aspirated 3 times 2100 c.c. removed	Faint heart sounds	0	110/80	+ Dependent Ascites	0°–100° 101°–102°	6,500	3½ mos.	Tbc. pericarditis with effusion. Miliary tbc. Pleural effusion, left	
16. 22 ♂	Shortness of breath. Pain in chest	12×4	+	+	0	0	110/70	0	100°–101°	9,600	3 mos.		Recovered. Dextrocardia
17. 52 ♂	Fever; abdominal distention	10.5×9	0	+	0	0	115/90–95/80	+ Ascites	99°–101°	9,000	7 mos.		Tbc. peritonitis. Tbc. pericarditis with effusion. Cirrhosis of liver ?
Terminal													
18. 46 ♂	Sense of constriction across chest 3 mos.	14×3	0	0	0	0	220/118	+	99°	14,400	3 mos.	Tbc. pericarditis. Tbc. mediastinitis. Chronic nephritis	Terminal in hypertension with chronic nephritis
19. 55 ♂	Nausea and vomiting 3 wks. Ascites 2 wks.	12×3	0	0	0	+ Auricular fibrillation	80/50	+ Dependent Ascites	98°–101°	4,000–15,000	7 wks.	Tbc. pericarditis	Terminal in cirrhosis of liver
20. 70 ♀	Weakness and dyspnea 3 wks.	11×3	0	0	0	Auricular fibrillation	105/65	0	98.6°–99.2°	12,500	3 wks. +	Tbc. pericarditis. Cirrhosis of liver. Pulmonary tbc.	Terminal in cirrhosis of liver

tuberculosis. Thrombosis of the femoral vein and a pulmonary infarct were seen, each once.

TABLE II

Age Distribution of Patients with Tuberculosis of the Pericardium

Age	Number of Cases
0–9	0
10–19	0
20–29	4
30–39	0
40–49	3
50–59	4
60–69	3
70–79	5
80+	1
Total	20

It would appear that tuberculosis of the pericardium may produce a massive effusion or a thick productive exudate. When death occurs at this stage, tuberculous tissue is abundant and easily recognized. When the lesion heals, there is organization of the granulation tissue with or without calcification.

Under the term primary tuberculosis of the pericardium, there are described cases [1] in which the pericarditis seems to be the oldest and, in some, the only tuberculous lesion found at necropsy. In the present series of cases, the lesion in the pericardium appeared to be the oldest in twelve. In several the pericardium had become involved as a result of a rupture of a caseous lymph node directly into the pericardial sac. In others, there was evidence that the process had extended to the pericardium from the pleura, the lung, or even the peritoneum. Since practically all infections of the serous membranes result from an extension of an infection directly to them, it is not surprising to find that pericardial tuberculosis arises in this way. When the lesion of the pericardium is the oldest one and the disease is confined to the pericardium, death results from the signs of a wasting disease or cardiac insufficiency, or it may be found accidentally during the course of another disease. Very often, however, the process spreads beyond the pericardium so that there is multiple serous membrane involvement or miliary tuberculosis. In these, the clinical picture is that of multiple serous membrane tuberculosis, cardiac insufficiency, or miliary tuberculosis, or all three. These various aspects of infection will be taken up separately.

GENERAL FEATURES

Fever. The febrile reaction was a conspicuous feature in 13 of the 20 cases. It was the outstanding characteristic of the patients with only the signs of a wasting disease and equivocal pericardial signs. In the patients with circulatory failure with congestion, fever was absent in four of the

eight cases. In those with a pericardial effusion, only one remained fever-free during the period of observation. In two of the cases in which the condition was latent and therefore probably terminal, there was no fever. In the febrile cases the daily fluctuation ranged between 99° and 101°, 102°, or even 103°. In essence, then, the presence of irregular fever in patients with heart failure, especially elderly individuals with signs suggesting pericardial disease, should point toward the possibility of tuberculosis of the pericardium.

White Blood Cell Count. Anemia was not a feature in these cases. The red blood count and hemoglobin content were reduced in four. In the others they were normal. One patient had chronic nephritis. As is the case in other types of tuberculosis, there was nothing absolutely characteristic about the total white blood cell count. There were wide variations. It was below 5,000 in five, between 5,000 and 10,000 in seven, 11,000 and 15,000 in five, and above 15,000 per cubic millimeter in three. There was nothing distinctive about the differential count although the lymphocyte-monocyte ratios were not studied in detail.

Cardiac Arrhythmias. Auricular fibrillation was present in three cases, partial heart block in one. In the others, there were no detectable abnormalities by physical examination. It was not uncommon to observe a low voltage with inversion of the T-waves. Paroxysmal auricular fibrillation has been observed by Dillon,[3] and others.[4]

Signs of Congestive Heart Failure. There was peripheral edema in 10 cases, ascites in eight, and pleural effusion in nine. In seven of the nine cases of pleural effusion, it was finally demonstrated that tuberculous pleurisy was present, so that one was in fact dealing with multiple serous membrane infection. The pleural effusion was unilateral in five, bilateral in three, and interlobar in one. In two cases such effusions were present without peripheral edema or ascites. In both of these cases the pericardial involvement was indicated by a well marked friction rub, and in one the interlobar pleurisy with effusion was discovered only by roentgen-ray examination. In three cases the pleural effusion was due to venous stasis, as attested by the character of the fluid, and by the absence of tubercles in the pleura at necropsy. In one of these cases there was an effusion on one side due to venous stasis and a productive tuberculosis on the other side. In the remaining five cases, which include one of the previous group where both stasis and tuberculosis were present, there was tuberculosis of the pleura to account for the effusion.

Of the eight cases showing ascites, two showed no peripheral edema; in one the ascites was due to tuberculosis of the peritoneum. In six, the ascites was a part of the general edema.

Summing up, then, it can be asserted that the edema may be general. When there is an associated pleural effusion with or without peripheral edema, it is highly probable that there is an associated tuberculosis of the

pleura. This can usually be determined with precision by studying the aspirated pleural fluid.

When ascites exists it is seen most often in association with peripheral edema, and the fluid has the characteristics of a transudate. Much more rarely, the effusion is due to tuberculosis of the peritoneum, but one may see cases with evidence of heart failure, with tuberculosis of the pericardium and of the pleura, and with a transudate in the peritoneal cavity. Only after a careful study of the fluid can the final decision be reached. Predominant ascites as a manifestation of heart failure was present in only one case in this group.

Blood Pressure. In pericardial disease, especially when there is cardiac compression, it is not infrequent to find a low systolic blood pressure and a low pulse pressure, particularly when the signs are acute. If one excludes two cases in which there was an associated hypertension, the blood pressure in this group was normal or below the average accepted normal for the age group. The systolic pressures varied from 90 to 135 mm. of mercury, and the diastolic pressures from 50 to 88 mm. of mercury. It is obvious that there is nothing absolutely characteristic about the average blood pressure findings. More important in diagnosis is a gradually declining blood pressure with a small pulse pressure, in the face of a rising venous pressure. These are indications of cardiac compression and should direct one's attention to the pericardium.

Pulse Rate. Increase in the pulse rate was the rule, 100 to 120 per minute being common. This is understandable on two grounds: first, because the metabolic requirements are increased due to the infection and, second, because it is only by means of an increased rate that the heart can maintain the output per minute when there is a decrease in diastolic filling. Pulsus paradoxicus was noted on several occasions.

Local Signs Over the Pericardium. The points of diagnostic importance in the physical examination are the determination of the size and configuration of the heart, the presence or absence of a friction rub, the presence of arrhythmias or murmurs, and the quality of the breath sounds. In this group of 20 cases, the transverse diameter of the heart, as determined by roentgen-ray examination, varied from 14 to 22 centimeters. The most conspicuous widening was present in those individuals showing effusions, of which there were seven. True dextrocardia was existent in one. The amount of fluid varied from 700 to 3,500 cubic centimeters. A friction rub was heard in only five cases, and it persisted anywhere from two days to three weeks. The apex beat was either feeble or not obtainable, and the sounds distant and faint. Murmurs were absent, and arrhythmias were present in three cases. These signs then may be summed up by saying that the important ones are an increase in the transverse diameter of the heart, the signs of an effusion, a pericardial friction rub, and a feeble apex beat with distant heart sounds without murmurs.

Roentgen-Ray Examination. There is nothing characteristic in the roentgen-ray findings. There may be the classical signs of a pericardial effusion or merely a widening of the cardiac shadow. The fluoroscopic examination may reveal a diminished pulsation of the ventricles. This is more significant when the size of the heart is small, since it indicates an interference with diastolic filling.

The Character of the Pericardial, Pleural, and Ascitic Fluid. The fluid may be straw-colored or hemorrhagic. When there is a simple transudation of fluid due to venous stasis, the fluid has the characteristics of a transudate. There is one condition, however, in which a transudate assumes the characteristics of an exudate, insofar as the protein content is concerned, and that is following a copious diuresis that has been induced by drugs. I have seen the protein content of a pleural fluid increase from 1 to 4.5 per cent following diuresis. The circumstances under which the fluid is examined must therefore be taken into account.

The fluid may be hemorrhagic and, in this respect at least, resemble the fluid from rheumatic fever exudates, or from those resulting from metastatic tumors in the serous membranes. From experimental studies [5] we know that hemorrhagic fluids in tuberculosis are more likely to contain tubercle bacilli, since large numbers of tubercle bacilli injected into the serous membranes of a sensitized animal frequently result in a hemorrhagic exudate.

The presence of tubercle bacilli as determined by guinea pig inoculation or by direct examination makes the diagnosis positive. Without this, the fluid findings are not absolutely decisive. The important point to determine is whether the fluid is an exudate or a transudate, since in tuberculosis of the pericardium there may be a transudate or an exudate in the other cavities depending upon the presence of infection, or stasis, or both.

The cell count is increased and the cells are usually of the mononuclear or lymphocytic variety.

Symptoms. It is convenient for purposes of discussion to divide the cases into several groups, depending upon the symptomatology and the clinical course of the disease. This division is more or less arbitrary since one group may gradually begin to show the signs which are considered characteristic of another. This is not surprising since such merely indicate various phases of the same disease process. The outstanding clinical features depend upon the pathogenesis, mode of spread, the type of pathological process causing the functional disturbance, and the duration and stage of the disease. The following subdivision of cases has been adopted:

1. Patients with symptoms and signs of a wasting disease and obscure fever.
2. Patients with symptoms and signs suggesting heart failure with congestion.
3. Patients with symptoms and signs of multiple serous membrane tuberculosis.

4. Patients with symptoms and signs of a massive pericardial effusion.
5. Patients with symptoms and signs of miliary tuberculosis.

Patients with Symptoms and Signs of a Wasting Disease and Obscure Fever

There were five patients in which these signs were the outstanding features of the illness. The following case report is an example.

Case 12. A man, aged 70 years, complained of shortness of breath and weakness. His past and family histories were inconsequential and he had always enjoyed relatively good health. For a period of two years he had felt some constriction across his chest after exertion which was relieved by rest. Aside from this, he had no discomfort until two months before he was seen. At that time he began to notice progressive weakness, loss of weight, insomnia, and some shortness of breath on exertion. Several days before admission to the hospital he had some pain over the lower part of the chest which was not severe and did not radiate. The examination showed an elderly man, with moderate dyspnea, resting quietly. There was no orthopnea. He obviously had lost weight but his skin and mucous membranes were of normal color. The positive findings were confined to the examination of the heart. There was some tenderness of the skin over the precordium; the heart measured 10 centimeters to the left and 7 centimeters to the right of the mid-sternal line by teleroentgenogram. The sounds were distant but without murmurs, and the apical impulse was feeble. A short superficial friction rub was heard over the precordium. The blood pressure was 145 mm. of mercury systolic, and 65 mm. of mercury diastolic. The lungs were clear, the abdomen and extremities negative.

Laboratory Examinations. The electrocardiographic examination showed a normal mechanism with no abnormalities in conduction. There was no anemia, and the leukocyte count was 5,900 per cubic millimeter. The differential was normal.

Course of the Disease. After two days, the pericardial friction rub disappeared and never returned. The temperature was elevated, and varied from 100° F. to 103° every day. The patient showed signs of progressive weakness and loss of weight. The blood pressure did not change; there were no signs of congestive heart failure or increased venous pressure. The area of cardiac dullness remained wide and the heart sounds became more and more distant until they could be heard with difficulty. The apex beat could not be felt. He finally had an attack of rapid heart rate with collapse and died in coma. The total duration of his illness was 12 weeks from the onset of symptoms. The necropsy showed a tuberculosis of the pericardium with thick fibrinous exudate. The heart was of normal size. There were numerous enlarged mediastinal lymph nodes; one had extended directly into the pericardial sac. There were no signs of active tuberculosis elsewhere.

In brief, then, the salient features were those of a febrile illness in an elderly man, with a transitory pericardial friction rub and an increase in the area of cardiac dullness, a feeble apex impulse and distant heart sounds. His course was one of progressive weakness with the features of a chronic febrile wasting disease. Necropsy demonstrated that the sequence of events had been the rupture of a caseous mediastinal lymph node into the pericardial sac and an extensive tuberculous infection of the pericardium. At no time were there any signs of increased venous pressure.

These patients have the symptoms and signs which are common to any

chronic infection (fever, progressive weakness, loss of weight, anorexia, malaise, etc.). In addition, there may be symptoms referable to the chest, with pain and constriction over the precordium and shortness of breath. The physical examination may reveal a pericardial friction rub, but the chief features may be signs which are compatible with a thickening of the pericardium; i.e., feeble apex beat, distant heart sounds, and an increase in the transverse diameter of the heart. In any event, it should be recalled that obscure fever in the elderly may be due to a tuberculosis of the pericardium.

Patients with Symptoms and Signs of Cardiac Insufficiency

When there is a compression of the heart or great vessels resulting from an exudate in the pericardium, there is an obstruction to the inflow of venous blood, and circulatory failure with congestion follows. When pericardial disease appears in the elderly there is often another disease present, namely, coronary arteriosclerosis. The changes in the circulation which follow pericardial disease often increase the difficulty of supplying sufficient blood to the heart. The low mean arterial pressure, the low cardiac output, and low stroke volume will all tend to decrease coronary circulation. In addition, in some cases, as those reported by Bellet, Gouley, and McMillan,[20] there exists definite arteritis with occlusion of the coronary vessels which would naturally decrease the coronary circulation further. It is not surprising, then, that once circulatory failure sets in it is progressive and there is rarely any improvement. These patients complain of a sense of constriction in the chest on exertion that is relieved by rest. They exhibit edema, shortness of breath, cough, and progressive weakness. Early in the course of the disease there may be very little pulmonary congestion. The dyspnea in these cases is probably due in part to the increase in the venous pressure in the great veins through a reflex mechanism, as described by Harrison.[7] Later, there are signs of pulmonary congestion. But, as I have stated, effusions into the pleural cavity in active tuberculosis of the pericardium are likely to be due to an infection of the pleura rather than a transudate. Finally, the disease is not infrequently terminated by a miliary tuberculosis. In this group of eight patients with progressive heart failure, there was fever in four, pleural effusion in seven, tuberculosis of the pleura in five, ascites with edema in six, and ascites without edema in one. Miliary tuberculosis was present in three. The following case illustrates the course of events in a typical case.

Case 9. This white man, 74 years of age, was seen first in December 1934. At that time he complained of failing health for two or three months. This was characterized by weakness, shortness of breath on exertion, orthopnea, and edema of the lower extremities, genitalia, and abdomen. He had always enjoyed good health until the present illness.

The physical examination showed a small man with evidence of loss of weight. The skin was dry and scaly over the upper part of the trunk and arms. The mucous membranes were of normal color. The examination of the head revealed no abnormalities. The neck veins were moderately distended. The chest was small, moved

as a whole, and showed a senile kyphosis. There were moist râles at both lung bases, and the signs of a hydrothorax in the left pleural cavity. The heart borders were difficult to define by percussion. The apex beat was not visible or palpable. The sounds were distant and feeble in quality. There were no murmurs or friction rub. The aortic second sound was louder than the pulmonic second sound. The abdomen was distended with fluid, and there was a distinct fluid wave on percussion. No other abnormalities were found. There was massive pitting edema over the sacrum and back, lower part of the abdominal wall, and genitalia. The temperature was normal; the pulse rate varied from 100 to 110 per minute. The respirations were 32 per minute. The blood pressure was 110 mm. of mercury systolic, and 75 mm. of mercury diastolic.

Laboratory Examinations. The urine showed neither albumin nor sugar. The white blood cell count was 4,250 per cubic millimeter. The total protein of the blood plasma was 5.7 per cent. The ascitic fluid had the characteristics of a transudate. The specific gravity was 1.012. There were 23,000 cells per cubic millimeter, of which 500 were white blood cells and the remainder were erythrocytes. The differential count of the white cells showed 80 per cent lymphocytes and 20 per cent monocytes.

Roentgenogram of the chest showed the heart to be enlarged to the left, and there were signs of fluid at the left base. There was evidence of an old tuberculous process at both apices.

Electrocardiographic examination revealed a left ventricular preponderance with a low amplitude of the QRS complexes.

Course of Illness. The patient failed gradually for a period of 11 weeks. The usual treatment for congestive heart failure was unsuccessful in relieving his edema. During the last week of his illness there were fever, cough, and an increase in the râles throughout his lungs. He died five months after the onset of symptoms of heart failure. The anatomical diagnoses were: Tuberculosis of the pericardium—containing 300 c.c. of sero-sanguinous fluid; miliary tuberculosis of lungs, liver, spleen; coronary arteriosclerosis; cardiac enlargement.

To sum up, an elderly man developed heart failure with congestion which was progressive without remission over a period of five months. The entire course was afebrile except for the last week of his illness when there was irregular fever and cough. Necropsy demonstrated the cause of his illness to be due to tuberculosis of the pericardium and a terminal miliary tuberculosis.

Mechanism for the Production of Circulatory Failure with Congestion in Pericardial Disease

From the careful observations of a number of observers, we are now able to understand the mechanism which produces circulatory failure in patients with pericardial disease. Experiments have been done on animals with acute and chronic pericardial disease,[8, 9, 10] and quantitative studies of the circulatory functions have been carried out in man with the same disorder. The type of circulatory failure which is seen in pericardial disease has been called " inflow stasis " by Volhard.

In the case of an acute distention of the pericardium with an inflammatory exudate or with blood, the pericardium stretches very slowly so that

the increasing pressure within the pericardial sac causes cardiac compression, with a falling systolic blood pressure, a rising venous pressure, enlargement and depression of the liver. Beck [11] has stated that a pressure equal to 16 centimeters of water, acutely applied to the heart, may be fatal. This external pressure on the auricles interferes with the inflow of blood from the periphery and an inadequate filling of the heart results in insufficient output to maintain life. When the process in the pericardium is more chronic and produces compression of the heart by fibrous tissue, the pressure within the great veins may attain very high levels. Such individuals, in addition to the increased venous pressure, show enlargement of the liver with ascites. No cardiac enlargement is present, although it may be suggested by an increase in the transverse diameter of the heart.

From a quantitative study of the dynamics of the circulation in *concretio cordis*, Burwell, Strayhorn and Flickinger [12, 13] have stressed the following points. At rest, these individuals show a low pulse pressure, a rapid pulse rate, an elevation of the general venous pressure, a low circulatory minute volume, and a reduced stroke volume. The oxygen utilization is high but the oxygen saturation of the arterial blood is normal, and there may be a normal or only slightly reduced vital capacity.

Following exercise, the oxygen consumption increases but the pulse pressure and stroke volume remain unchanged. The pulse rate accelerates and the circulatory minute volume increases in proportion to the rate. Venous pressure increases and cyanosis is clearly visible.

The exhibition of digitalis causes a slowing of the rate and a decrease in the cardiac output. In brief, it appears that the only method of increasing the blood supply to the tissues is through increasing the heart rate. It is not possible to increase the stroke volume, since the heart is prevented from receiving more blood during diastole.

Patients with Symptoms and Signs of Multiple Serous Membrane Tuberculosis

It is common knowledge that tuberculous infections of the serous membranes are very often multiple. The results of the present study were confirmatory of this rule. As has been related already, seven of the patients had a tuberculous pleurisy, and one had an associated tuberculosis of the peritoneum. The finding of tuberculosis of the pleura or peritoneum may aid in the etiologic diagnosis of the pericardial lesion, particularly if the signs are equivocal and circulatory failure is present. The case report which follows indicates the course of events in one of the cases.

Case 7. An 81 year old man complained of pain in the back of three weeks' duration. His family and past histories were non-contributory. He regarded himself as well until a year before he was seen, when he had an infection which was called the grippe. It was characterized by malaise and weakness but there was no dyspnea. Since then he had had several small hemoptyses at varying intervals. A

few months before he was admitted to the hospital he began to notice dyspnea and tightness across the chest on exertion, which were relieved by rest. These symptoms progressed for three weeks; then he developed an acute respiratory infection with generalized aches, pains, and prostration. For a week he had experienced attacks of paroxysmal nocturnal dyspnea accompanied by cough. There were also weakness and anorexia.

The examination revealed a temperature of 101° F., pulse rate 98 per minute, respirations 24 per minute. The blood pressure was 105 mm. of mercury systolic and 75 mm. of mercury diastolic. He was a pale, elderly man with some increase in the respiratory rate without distress. The examination of the head revealed nothing abnormal. The lungs showed impaired resonance and râles at the base of the left lung. The right side of the chest revealed evidence of a pleural effusion. The heart was enlarged to both the right and left, the transverse diameter being 15 centimeters. The rate was rapid and totally irregular, the sounds were very faint, and all over the lower part of the sternum there was a to-and-fro friction rub. The liver was slightly enlarged below the costal margin; otherwise the abdomen was negative. There was no edema of the legs.

Laboratory Examinations. The urine was negative. The red blood cell count was 3,900,000 per cubic millimeter, hemoglobin 78 per cent (Sahli), and the white blood count was 7,400 per cubic millimeter. The Kahn reaction was negative. The non-protein nitrogen was 30 milligrams per cent, and the total protein of the blood plasma 5.2 per cent. The sputum was negative for tubercle bacilli. The pleural fluid had a specific gravity of 1.017. The cell count per cubic millimeter was as follows: red blood cells 3,810, lymphocytes 110, mononuclears 580. There was a great increase in the fibrin.

Course of Illness. After three days the temperature fell to normal and finally to subnormal after several weeks. With rest and digitalis the ventricular rate was reduced. The electrocardiogram showed auricular fibrillation and low voltage. The tuberculin test in a dilution of 1:1,000 was positive. The pericardial friction rub disappeared after two weeks. The heart sounds remained distant and weak. There were rapidly recurring effusions into the right chest. He failed gradually and died after a period of nine weeks' observation.

The necropsy revealed tuberculosis of the pericardium, bilateral tuberculosis of the pleura, and pulmonary tuberculosis with a small cavity in the right lung.

There was no doubt, in this case, that the process began in the lung and then extended to the pleura and pericardium. At no time were there signs of heart or circulatory failure. It was a clear example of serous membrane tuberculosis in an elderly man.

Patients with Symptoms and Signs of a Massive Pericardial Effusion

It is universally recognized that one way in which the pericardium responds to a tuberculous infection is by the exudation of copious amounts of fluid which is frequently hemorrhagic. A pericardial effusion was found in seven of the 20 cases and varied from 700 to 3,500 cubic centimeters. All but one had fever. Three of these patients showed circulatory failure, the other four did not. It is perhaps worthy of comment that the two patients in the entire group who survived were young, with a moderate collection of pericardial fluid and no signs of cardiac compression. In one the effusion was accompanied by tuberculosis of the peritoneum, in three there was an associated tuberculosis of the pleura, and in one the disease terminated with

a miliary tuberculosis. There was nothing peculiar about the physical signs of the pericardial effusion and they were all characteristic. It does not seem unreasonable to suppose that the patients who have a poor outlook in this group are those who develop cardiac compression or an associated tuberculosis of the pleura or peritoneum. Conversely, the ones who are likely to improve are young individuals with a small effusion, without cardiac compression or signs of tuberculosis elsewhere. The following case illustrates the course of events in these cases.

A man, 70 years of age, was apparently healthy until two weeks before entry to the hospital, when he had a sudden acute pain in the left side which was severe and exaggerated by respiratory effort. Soon thereafter, shortness of breath on exertion and edema of the legs and abdomen appeared.

Examination showed a man with moderate cyanosis but without respiratory distress. The head, nose, and throat revealed nothing abnormal. The veins of the neck were greatly distended. The lungs were everywhere clear except for a number of moist râles at both bases. The heart measured 17 centimeters in its transverse diameter. The apex beat was not palpable, the sounds were feeble and distant, and there was a loud friction rub over the precordium. The liver was enlarged 6 centimeters below the costal margin; the abdomen was distended with fluid. There was massive edema of the genitalia, legs, and feet. The temperature varied from 101 to 102° F. The pulse rate varied from 90 to 100, the respiratory rate from 25 to 40 per minute.

Laboratory Examinations. The urine showed a trace of albumin and a rare hyaline cast. The pericardial fluid was serosanguinous with 6,000 red blood cells per cubic millimeter and 400 white blood cells, of which 80 per cent were lymphocytes and 20 per cent were monocytes.

Course of the Disease. During the first seven weeks of observation the temperature was elevated for five weeks, and then remained normal for two weeks. The pericardium was tapped on three occasions, and 650, 1,000 and 400 cubic centimeters withdrawn. There was temporary improvement but by the ninth week his dyspnea and edema were increasing. The veins of the neck became greatly distended. The signs over the heart remained the same but there appeared definite evidences of an effusion of fluid into the left pleural cavity. The abdomen was distended, the liver enlarged, and the edema and cyanosis were generalized. There was a pleuropericardial friction rub. The fluid from the left side of the chest had the same characteristics as that from the pericardium. The temperature remained normal, the pulse and respiratory rate were elevated. He failed rapidly and died three and one-half months after the onset of symptoms.

The anatomical findings were: tuberculosis of the pericardium with an effusion of 550 cubic centimeters of serosanguinous fluid; tuberculous pleurisy with effusion of 900 cubic centimeters of fluid; generalized miliary tuberculosis of the lungs.

In a word, an elderly man with tuberculosis of the pericardium and a large effusion developed circulatory failure due to an increase in the general venous pressure. As the disease progressed, the left pleural cavity became involved and disseminated tuberculosis of the lung appeared as the final event. This case illustrates how a pericardial effusion may cause circulatory failure, and demonstrates the dangers of a spread to the pleura and of disseminated tuberculosis.

Patients in Whom Tuberculosis of the Pericardium Is a Terminal Event in the Course of Another Disease

There were three patients in whom tuberculosis of the pericardium was a terminal event; two had cirrhosis of the liver and one had chronic nephritis. Cardiac insufficiency was present in two, but there was no evidence that the pericardial lesion was responsible for the heart failure except in the one patient with cirrhosis of the liver. The latter case follows.

Case 14. This 55 year old man was first seen in October 1934 when he complained of anorexia, nausea, and vomiting of three weeks' duration. There had been frequent bowel movements for one week. The point of significance in his past history was the fact that he had used large amounts of alcohol for about 32 years.

The physical examination showed a man with fever which fluctuated between 99 and 101° F. every day. He had lost weight but did not appear pale. The lungs were clear and the heart was not enlarged. The sounds were clear and no friction rub was heard. The peritoneal cavity was filled with fluid. There was no edema of the legs.

Laboratory Examinations. The white blood count varied from 4,200 to 15,000 per cubic millimeter. The ascitic fluid on two occasions had the characteristics of a transudate; a specific gravity of 1.003, white blood count of 108 per cubic millimeter and red blood count of 372 per cubic millimeter. Roentgen-ray of the chest showed that the lungs were clear and the heart not enlarged. An electrocardiogram revealed left ventricular preponderance and auricular fibrillation.

Course of the Disease. Four weeks after he was first seen, he commenced to have shortness of breath, increasing anorexia, and edema of the legs and abdomen. He was slightly jaundiced and râles appeared at the lung bases. The heart reverted to a normal sinus rhythm with a partial heart block. The edema progressed and he died two weeks later.

The necropsy findings were: tuberculosis of pericardium; alcoholic cirrhosis of the liver; chronic duodenal ulcer; ascites.

In this case, the tuberculosis of the pericardium was a terminal event in a patient with cirrhosis of the liver. The cirrhosis was outstanding.

Patients in Whom Tuberculosis of the Pericardium Is Followed by Miliary Tuberculosis

Disseminated tuberculosis following tuberculous infection of the pericardium is not infrequent. It was present in five of our cases. The cases in which the pericardium was involved as a part of a disseminated infection were, of course, not included in this study since they gave no evidence of pericardial disease during life. Others have commented on the frequency with which tuberculosis of the pericardium is followed by dissemination of the disease and this sequence undoubtedly is responsible in part for the high mortality. In some cases the whole course of the disease is afebrile and the finding of miliary tubercles everywhere comes as a complete surprise.

Comment

Taking the evidence as a whole, the clinical features of tuberculosis of the pericardium may be reviewed as follows. The diagnosis should be entertained, especially in elderly individuals, when there are symptoms and signs of an infection with localizing signs indicating a lesion of the pericardium. There may be only a pericardial friction rub of short duration, or unmistakable evidence of a pericardial effusion, and of cardiac compression with peripheral venous stasis and edema. It perhaps should be emphasized that in some patients the signs of infection predominate and the evidence for a lesion of the pericardium is very meager. It may consist only of a feeble apex impulse and distant heart sounds, signs which, in themselves, are certainly not always compatible with disease of the pericardium. It is also worthy of comment to say that there may be the signs of " inflow stasis " or peripheral edema indicating pericardial disease without signs of an acute infection.

If the process spreads from the pericardium to the pleura or if there are signs of tuberculosis of the peritoneum or the lungs at the same time, then the diagnosis is much simpler. Finally, one should remember that miliary tuberculosis in the elderly may begin as tuberculosis of the pericardium.

Differential Diagnosis. In my experience, the diseases with which tuberculosis of the pericardium have been confused most often are: (1) coronary artery disease with consequent heart failure, (2) cirrhosis of the liver, (3) rheumatic pericarditis.

Coronary Artery Disease. In elderly individuals who complain of constriction in the chest and symptoms suggesting cardiac insufficiency without evidence of valvular disease or hypertension, the diagnosis of coronary artery disease is most often entertained. If this is accompanied by precordial pain that is followed by fever and a pericardial friction rub, the temptation to make the diagnosis of a coronary occlusion with myocardial infarction is great. Even in the absence of a friction rub, the signs over the heart may be similar in the two conditions under discussion; that is, the heart sounds are distant and the apex impulse feeble. This is particularly true of patients with coronary occlusion who have developed an aneurysm of the left ventricle following infarction. One point of difference may be helpful in these cases. The impulse after coronary occlusion is more likely to be well felt but the heart sounds are feeble and there is often a gallop rhythm present; whereas in pericardial disease, the apex impulse and the sounds are both distant. In addition, the roentgen-ray diagnosis of an aneurysm of the left ventricle may aid in the differentiation.[14] The electrocardiogram may be helpful but it is not always decisive since changes in the T-waves similar to those occurring in coronary occlusion are reported in cases of pericardial disease. The differentiation must be made largely on the basis of the clinical course of the disease, a careful analysis of the history, and the various physical and other findings.

Cirrhosis of the Liver. Inasmuch as two of the cases described had an

alcoholic cirrhosis of the liver and a terminal tuberculosis of the pericardium, both conditions may coexist in the same individual. In the one case, the cirrhosis was limited in extent and therefore latent. In the other, the symptoms and signs were predominantly those of cirrhosis, and the diagnosis of tuberculosis of the pericardium was latent and disclosed by the pathologist.

The instances in which tuberculosis of the pericardium is likely to be confused with cirrhosis of the liver are those in which there is an insidious onset with progressive signs of stasis, and ascites which is disproportionate to the other evidences of increased venous pressure. This is the picture that is seen most often in *concretio cordis* with or without calcification of the pericardium, and it is not seen so often in the more acute type which has been described in this paper.

It is convenient at this point to say something about so-called " cardiac cirrhosis," since this is the condition seen as a result of repeated attacks of heart failure and chronic venous stasis. It should be clearly distinguished from other types of hepatic cirrhosis, since it is highly doubtful whether the alterations in the structure of the liver in chronic stasis are of sufficient degree to cause portal obstruction. It consists of a central necrosis, usually of the hemorrhagic type. The necrotic cells are removed by macrophages and, if no regeneration takes place, the stroma of the liver gradually contracts, resulting in areas of sclerosis around the central veins. As a result of this process the liver is diminished in size and its surface finely and evenly granular. It is to a liver at this stage that the name " cardiac cirrhosis " has been given.

In a certain number of cases, perhaps due to a stimulus of an unusually extensive central necrosis or repeated attacks of congestion, very active regeneration of liver cells takes place. If these areas of regeneration surround the sublobular veins, they tend to be roughly circular in outline. If they follow the radicles of the portal vein, they have a curious branching arrangement which has been likened to a fern leaf. When Youmans and Merrill [15] collected and reported the cases of pericarditis calculosa several years ago, they called attention to the fact that at least one-third of the reported cases were associated with an " atrophic " cirrhosis of the liver. They were not of the opinion that the cirrhosis of the liver in these cases resulted from chronic venous stasis, but that it was a further expression of the fundamental disease process which, in most cases, was tuberculosis. Without more details of the histologic changes in the liver being available, it is impossible to say whether the changes observed in the liver in cases of pericarditis calculosa are the result of chronic stasis or not.

One of the most reliable tests for discriminating between cirrhosis of the liver and " inflow stasis " is the general elevation of venous pressure. That is to say, the venous pressure is increased in both the veins of the upper and lower extremities in pericardial disease, whereas in cirrhosis of the liver the venous pressure of the legs may be increased in the presence of ascites but

the pressure in the veins of the arms is normal or only slightly elevated. The presence of other signs of portal obstruction is often more conspicuous in cirrhosis of the liver. It is perhaps worthy of comment that patients with limited cirrhosis of the liver may die of heart failure, as in the cases reported by McCartney.[21] This was true in 25 per cent of the cases. In most of the cases the cirrhosis of the liver played no part in the clinical picture.

One may sum up the discussion by saying that patients with latent or advanced cirrhosis of the liver may develop tuberculosis of the pericardium as a terminal event. It is also recognized that venous stasis resulting from pericardial disease may produce secondary anatomical changes in the liver. The relative importance of these changes in the production of ascites cannot be assessed at present. Certainly, recurrent ascites is observed without any change in the liver other than chronic passive congestion. Finally, it is not uncommon for patients with latent cirrhosis of the liver to die as a result of independent heart disease. The cases in which confusion most often arises are those with recurrent ascites and an increase in general venous pressure. The last feature is of the highest importance in differential diagnosis.

Rheumatic Heart Disease. The appearance of tuberculosis of the pericardium in the younger age groups requires differentiation from rheumatic heart disease. In some this is not difficult, especially if there is an associated arthritis or if there are signs of valvular disease, or changes in conduction by electrocardiographic examination. When tubercle bacilli can be obtained from the pericardial fluid or when tuberculosis exists elsewhere then the diagnosis is less difficult. However, when the fluid fails to contain demonstrable tubercle bacilli it is not possible to make the discrimination on the basis of the characteristics of the fluid alone. They both have the characteristics of an exudate, contain large amounts of fibrin and an increase in cells, and both of them may be hemorrhagic. In a few, the diagnosis can be made only from a study of the course of the disease. I have seen several patients who had been sent to tuberculosis sanatoria on account of pleurisy and pericarditis with a hemorrhagic fluid who returned after two years with unequivocal signs of mitral stenosis. This was excellent testimony that the original disease was rheumatic fever.

It is perhaps well to recall that while disturbances in rhythm or conduction are not common in tuberculosis of the pericardium, they have been observed, so that this sign alone does not favor the diagnosis of rheumatic heart disease. It has been suggested by Bellet, Gouley, and McMillan that the presence of arrhythmias may suggest tuberculous disease of the heart muscle, especially of the right auricle.

Speaking broadly, the diagnosis of rheumatic pericarditis may not be difficult in most cases; in the few in which tuberculosis is suspected, the various points mentioned above should prove helpful.

Prognosis and Treatment

From the study of these cases and others reported, it is difficult to escape the conclusion that tuberculosis of the pericardium is a most serious disease. The reasons would appear to be the age at which it is common, the tendency to multiple serous sac infection or disseminated tuberculosis, and the fact that the location of the lesion interferes with the functions of the circulation. That some patients recover and survive a number of years without difficulty, there seems to be little question. But even when there is healing of the pericardial lesion the end result may be cardiac compression resulting from the constriction of the heart by fibrous tissue with or without calcification.

Within recent years, striking advances have been made in the surgical treatment of *concretio cordis*.[10, 11, 13, 16, 17] The best results have been obtained in relatively young individuals who have a fibrous pericardium without signs of an active infection. In the cases of *concretio cordis* in which *active* tuberculosis has been found at the time of operation, the results have been unsatisfactory. Although the reported experience with surgical treatment is limited, it would seem justified to say that operation in the face of an active infection has little to offer.

Another method that has been used is the injection of air or oxygen into the pericardial cavity following the aspiration of fluid.[18, 19] The purpose of this is to prevent the development of adhesions. The only case in which I have seen this method used resulted in failure and the patient died.

There is no doubt that the pericardium should be tapped in the patients who show signs of cardiac compression, provided the compression is due to a pericardial effusion and not a fibrous exudate. A falling systolic pressure, a rising venous pressure, and clinical signs of venous stasis are indications for pericardial tapping.

Summary and Conclusions

From a study of 20 cases of tuberculosis of the pericardium, the following conclusions are justified.

1. Tuberculosis of the pericardium is seen most often in patients over 40 years of age, and it is essentially a disease of the elderly.
2. Patients frequently present themselves with:
    a. Symptoms and signs of a wasting disease and obscure fever.
    b. Edema and congestion simulating cardiac insufficiency.
    c. Multiple serous membrane infections.
    d. Miliary tuberculosis.
3. It may occur as a terminal event during the course of another disease.
4. The diagnosis may be entertained when there are:
    a. Symptoms and signs of an infection.
    b. Localizing signs over the pericardium, such as—

(1) Pericardial friction rub.
(2) Pericardial effusion.
(3) Signs of thickening of the pericardium.

c. Signs of circulatory failure which is predominantly of the "inflow stasis" type.

d. Signs of extension of the process to the other serous sacs, or a disseminated tuberculosis.

5. It may be confused with:

a. Coronary artery disease.

b. Cirrhosis of the liver.

c. Rheumatic pancarditis.

6. Tuberculosis of the pericardium arises from an invasion of tubercle bacilli from the mediastinal lymph nodes, the lungs, the pleura, or peritoneum.

7. The prognosis is always serious, and present methods of treatment are unsatisfactory.

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FULMINATING SEPTICEMIA ASSOCIATED WITH PURPURA AND BILATERAL ADRENAL HEMORRHAGE (WATERHOUSE–FRIDERICHSEN SYNDROME); REPORT OF TWO CASES WITH REVIEW OF THE LITERATURE *

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The occurrence of adrenal hemorrhages of varying degree is a matter of common clinical and pathological knowledge in such conditions as diphtheria, scarlet fever, measles, and pneumonia. In new-born and still-born infants, adrenal hemorrhage, likewise, is known to occur and is chiefly of mechanical or traumatic origin. Snelling and Erb[1] found 43 cases of adrenal hemorrhage in 3,637 consecutive autopsies, an incidence of 1.19 per cent. Of these, 15 occurred in the new-born. In older children adrenal hemorrhage is usually of toxic or infectious etiology.

The association of fulminating purpura with bilateral adrenal hemorrhage has long been recognized. The earliest case reports of this condition are to be found in the English literature. Garrod and Drysdale,[2] Voelcker,[3] Still,[4] Batten,[5] Talbot,[6] Blaher and Bailey,[8] were among the first to note this association, but it remained for Graham Little,[9] writing in 1901, to recognize and classify such cases as a distinct clinical entity. Waterhouse,[10] in 1911, reported one case and collected 15 from the literature. He attempted to portray a definitive disease picture, but added no knowledge as to the etiology beyond observations concerning a possible bacterial cause, which even earlier observers had suggested. Friderichsen,[11] in 1918, in an inclusive review, brought the literature up to date. His clinicopathological picture was quite complete, but he, likewise, added no new information concerning etiology. McLagan and Cooke,[12] in 1916, were perhaps the first to incriminate the meningococcus in two case reports, which fit definitely into the so-called Waterhouse-Friderichsen picture. Since that time there have been several other reports, chiefly in the German literature, notably those by Baumann, 1931,[13] Glanzmann, 1933,[14] and Bamatter, 1934.[15] The literature is brought up to date by Aegerter [16] in a recent excellent review. He has collected 55 case reports which fit into the clinical picture of this syndrome and in addition presents two of his own. To these may be added three cases presented in a study of meningococcemias by McLean and Caffey [17]; another reported by Glanzmann [14] and two cases in a series of suprarenal hemorrhages studied by Snelling and Erb. [1] Foucar [26] in a recent report adds still another case which presents a typical Waterhouse-Friderichsen picture.

The sequence of events occurs with sufficient regularity to enable one to

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paint a picture which stamps this syndrome as a clinical entity. The majority of cases occur in young children. In the reported cases the ages varied from two months to nine years with only seven, or approximately 10 per cent, occurring in adults. Forty-five, or 70 per cent, occurred in infants two years or younger. Sex apparently plays no part since the cases occurred with equal regularity in males and females.

The case history, characteristically, tells of a previously healthy child who quite suddenly becomes ill. The early symptoms are non-specific and are such as may occur in any acute infection. Many of the histories state that the child, having gone to sleep, apparently quite well, awakens suddenly during the night with a cry. Vomiting occurs early and frequently but is moderate, and the character of the vomitus is not notable. Hyperpyrexia is present and most cases report a septic type of fever with the upper levels as high as 108° F. Chills occur, but are present infrequently. Diarrhea and abdominal pain, never localized, are, likewise, present occasionally. Central nervous system symptoms appear early and vary from severe headache, in adults, to delirium, restlessness and generalized convulsions in children. The patients soon lapse into a lethargic, stuporous state and remain so until exitus occurs.

Within a few hours after onset a striking cyanosis is noted. This is mentioned in 29 case reports, or 46 per cent, and in two others a peculiar alternation of pallor and cyanosis is reported. The cyanosis is quite out of proportion to the degree of pulmonary involvement; but together with the tachypnea and dilatation of the alae nasae, it has often led to an erroneous diagnosis of pneumonia.

Soon after the appearance of cyanosis a petechial eruption is noted, involving the face, neck, trunk and extremities. The petechiae are bluish-red in color, irregularly shaped, and do not fade on pressure. The conjunctivae often present similar petechiae. They appear quite suddenly and soon become associated with a diffuse, macular, purpuric rash. This latter frequently tends to become confluent and form areas often as large as the palm of one's hand. The skin, thus, has a mottled, livid appearance, not at all unlike postmortem lividity. This rash persists until death occurs.

Examination of the patient reveals an extremely toxic, often comatose child, breathing rapidly and shallowly. The respirations occasionally change in character and become stertorous and of a Cheyne-Stokes variety terminally. At the onset of the illness, the pulse is proportionate to the hyperpyrexia, but later it becomes running, feeble and thready. Physical examination of the chest may reveal moist râles, posteriorly, at the bases. There is no change in cardiac contour, nor does auscultation reveal any changes beyond a sinus tachycardia and enfeeblement of the heart sounds. The abdomen is negative to examination. The extremities reveal only the characteristic rash described above. There are no characteristic neurological findings. Headache may be present and is often quite severe in

adults. Cervical rigidity is usually absent, or there may be the faintest suggestion of meningismus present. The reflexes are unaltered as a rule.

These dramatic events run their course in from 24 to 48 hours. The majority of cases terminate in 24 hours or less. Other less frequent findings are mentioned in occasional reports, such as a disparity between the high oral and rectal temperatures and a low surface temperature; tremors of the extremities and muscle flaccidity; all as variants from the usual picture.

The laboratory offers little help in diagnosis aside from the possibility of finding meningococci in blood smears from purpuric areas as suggested by McLean and Caffey,[17] Netter, Salanier and Wolfrom.[18] The former workers were able to demonstrate intracellular gram-negative organisms in smears from the skin lesions in 83 per cent of a series of cases of meningococcus meningitis.

Because of the fulminating character of the disease there are few detailed reports of the blood picture. There is usually a leukocytosis. Varying figures are given from 7,000 to 88,500, the average being about 12,000. There is a definite increase in granulocytes with a shift to the left. Three reports mention platelet counts: Battley[19] 216,000, Glanzmann mentions a thrombopenia but gives no figure, Bamatter, 172,000. Generalizations cannot be made from these three figures, but in view of the subcutaneous vascular lesions it appears that an adequate explanation of the purpura is at hand without calling upon a thrombocytopenia.

Spinal fluid examination usually reveals a clear, colorless fluid with perhaps a slight increase in cells, usually polymorphonuclears. Various other constituents of the fluid, such as globulin and sugar, show no change. Aegerter notes that of all the patients who were tapped only six showed abnormalities. In three there was an increase in cells, in six the meningococcus was isolated, and in four an increase in pressure was present.

Pathology

The outstanding pathological finding is a massive, bilateral adrenal hemorrhage. This was present in approximately 95 per cent of the cases. Occasionally only one adrenal is involved and, when so, it is usually the right. The hemorrhage may vary from multiple, pin point areas to a massive type, converting the adrenal into a "blood cyst." Almost always it is confined within the limits of the capsule of the gland. In only one of the reported cases was rupture noted to have occurred with a resultant hemorrhagic peritonitis.

The histopathology of the adrenals usually merely confirms the gross findings. The densest hemorrhage appears to be in the region of the medulla and zona reticularis of the cortex. It apparently involves the other layers by diffusion and often leaves a narrow layer of cortical tissue in the zona glomerulosa intact. Thrombosis or embolism is rarely seen and an inflammatory reaction is usually absent.

The skin lesion is apparently due to direct involvement of capillaries and arterioles by the causative organism. Brown [20] found an inflammatory reaction in the capillaries and arterioles of the subcutaneous tissue and corium with a perivascular leukocytic infiltration, in cases of meningococcus septicemia. Injury to vessel walls allows an escape of red cells, thus accounting for the purpuric eruption.

Examination of the brain reveals only a congestion of the superficial vessels of the leptomeninges. This is true even in the cases of definitely proved meningococcal etiology.

Other pathological findings are merely such as would occur with an acute infection. Namely: Cloudy swelling of the parenchymatous viscera, acute splenic tumor and often a terminal pulmonary edema and congestion. A finding of perhaps more importance is the frequent occurrence of an enlarged thymus, prominence of the mesenteric lymph nodes, hyperplasia of Peyer's patches and solitary lymphoid follicles of the intestines. Sixteen cases in the literature were reported to have enlargement of Peyer's patches and lymph nodes. Ten specifically mention enlargement of the thymus. This thymolymphatic prominence has been pointed out by Rabinowitz [21] and Bamatter.[15] The latter, in fact, believes it to be a factor of some importance in the pathogenesis of this disease, in view of recent work showing a definite correlation between status thymolymphaticus and adrenal hypoplasia.

Etiology

The determination of etiology presented difficulty to the early observers of this syndrome, perhaps because of its inherently fulminant character. Bacterial infection was early indicated as the probable cause, but a variety of organisms was found. Dudgeon [22] found a *Staphylococcus aureus* in one case and a pneumococcus in another. Graham Little was able to demonstrate streptococci in sections of the skin. Waterhouse's case yielded a negative postmortem spinal fluid and blood culture, and he reported that in most cases cultures had been sterile. It is interesting to note that at the time of Friderichsen's report only 12 cases included data on blood culture. Of these, seven were sterile and the others included the variety of organisms mentioned above. McLagan and Cooke's [12] work, already referred to, is the first report to incriminate, definitely, the meningococcus. Herrick [23] has emphasized the fact that it is in the fulminating type of meningococcal infection that a striking purpura is most apt to be found. It is, moreover, in this type of case that adrenal hemorrhage is seen, rather than in the usual manifestations of meningococcus infection. It may be argued that the involvement of the skin and adrenal medulla, both of similar ectodermal origin, is an evidence of the ectodermal tropism of the meningococcus. The pneumococcus, likewise, possesses an ectodermal or epithelial tropism and, moreover, is capable of producing purpuric skin lesions as demonstrated by Mair [24] and Julianelle and Reimann.[25]

Since McLagan and Cooke's report 21 cases, in the data of which definite statements as to etiology are included, have been added to the literature. Of these, 12, or 60 per cent, were due to meningococci. The others, constituting 40 per cent, either gave sterile cultures or growths of *Streptococcus hemolyticus* were obtained (Snelling and Erb). It is interesting to note that Bamatter, in 1934, found that only four bacteriological examinations had been done ante-mortem. Since then, three additional ante-mortem investigations have yielded meningococci. It seems, then, that the meningococcus is the most frequent, but not the only etiological agent found in this condition.

I should like to add to the total of 64 reported cases, two which recently occurred at the University Hospital.

Case Reports

Case 1. C. H., white, female child, aged four years, admitted to the Pediatric service at the University Hospital on April 6, 1936, with a complaint of pain in the side, chills and vomiting. The past and family histories are completely non-contributory. The child had been entirely healthy until onset of the present illness. Two days prior to admission the child's mother had noticed a slight cough. On April 5, 1936, one day prior to admission, there was a slight nasal mucoid discharge. The child went to bed at 8:00 p.m. after having eaten a light supper and appeared quite well. At 11:00 p.m. she suddenly awakened with a cry and complained of pain on the right side of the chest. Soon afterward she experienced a chill, and vomiting occurred. The child remained restless, feverish and disoriented throughout the night. At 6:40 a.m. there was a generalized convulsion which lasted about five minutes. She was seen by a physician who advised immediate hospitalization. On the way to the hospital another convulsion occurred.

When seen in the hospital the child appeared extremely toxic, temperature 104° F., respirations rapid and shallow, and pulse averaging 165 to 180 per minute, characterized as thready and of poor volume. At this time over the chest could be seen numerous purpuric spots, limited to the right side and apparently distributed along the intercostal spaces. The child was lethargic, but her attention could be attracted. On physical examination the following important findings were noted: Several petechial hemorrhages in the conjunctivae, dilatation of the alae nasi with respiration, injection of the pharynx and fauces. Examination of the chest revealed it to be resonant, but on auscultation the breath sounds were broncho-vesicular and there were fairly numerous moist and crepitant râles at the bases, posteriorly. Aside from the tachycardia and feebleness of the pulse, thè cardiovascular system was negative. The abdomen was distended, but showed no other changes. The reflexes were present and in the case of the patellar were even hyperactive. No cervical rigidity or other signs of meningeal irritation were present.

The blood picture, on admission, showed 3,000,000 red blood cells, hgb. 80 per cent, a total white count of 7,000 with 80 per cent polymorphonuclears and 20 per cent lymphocytes. Spinal fluid examination revealed a clear, colorless fluid containing 26 cells per cu. mm., predominantly polymorphonuclears. Blood culture, immediately after admission, showed a profuse growth of *Neisseria intracellularis*. Agglutination with polyvalent anti-meningococcus serum was markedly positive up to a dilution of 1:1560.

The child was put to bed immediately after admission and intranasal oxygen was started. In spite of sponges the temperature rose to 107.6° F. At the height of the

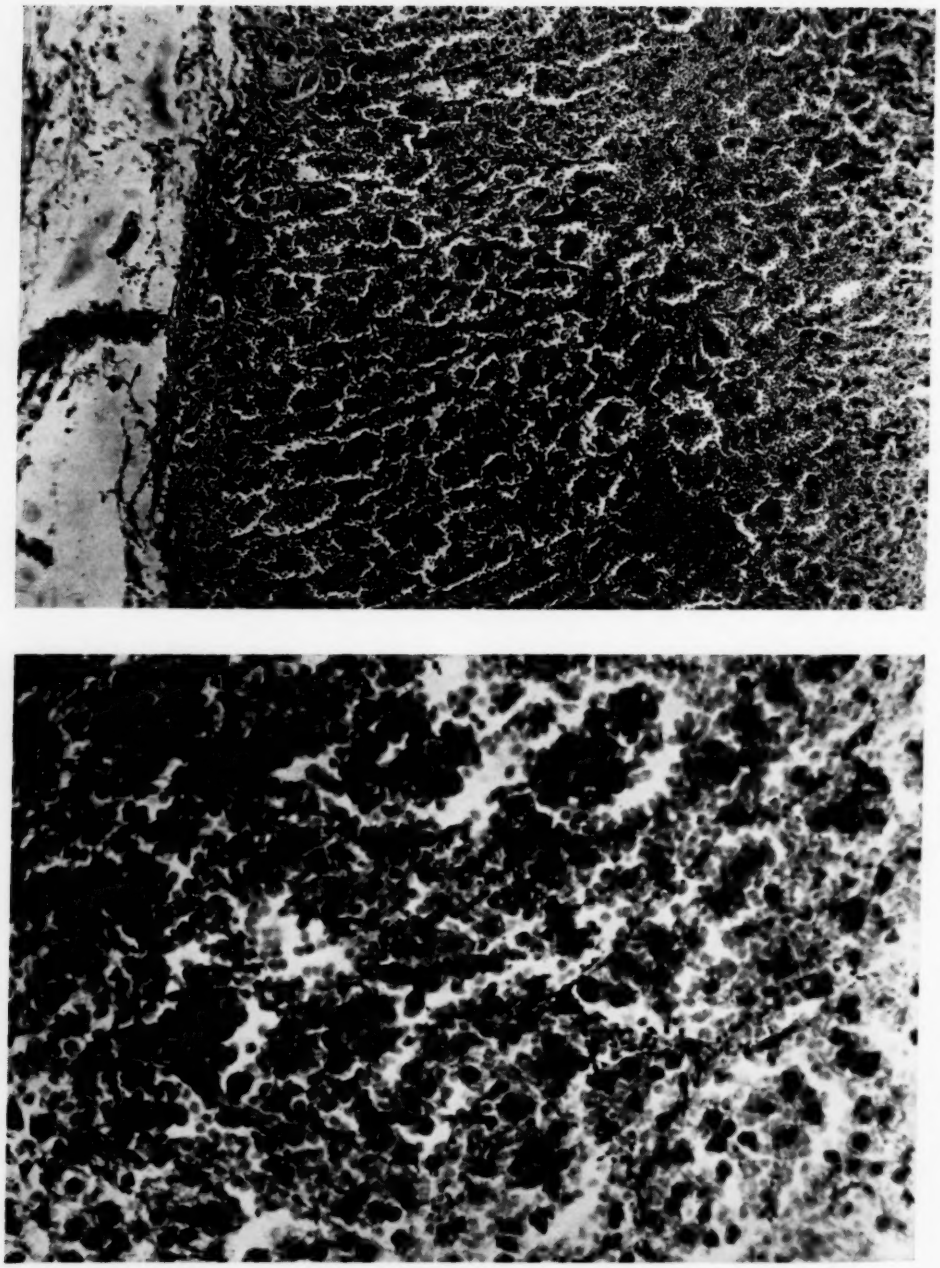

FIG. 1. Low and high power photomicrographs of the adrenal (case 1), showing extensive hemorrhage and destruction of parenchyma.

fever a macular, purpuric eruption appeared on the face, neck and lower extremities. Cyanosis of the hands, feet and back was quite pronounced. Respirations became slower and more labored. About one-half hour before death the child vomited about 200 c.c. of liquid black material, which gave a positive chemical reaction for blood. In spite of all medications death occurred at 5:30 p.m., April 6, 1936, approximately 18½ hours after onset.

An autopsy was performed two hours following death. The body was that of a well-developed and well-nourished child, showing a macular, petechial and purpuric eruption, most marked over the anterior chest. Numerous petechiae were seen in the bulbar conjunctivae. The mesenteric lymph nodes were prominent and had a reddish tint. The thymus was of normal size and presented no gross pathologic change. The lungs, liver, kidneys, heart, pancreas and gastrointestinal tract revealed no gross or microscopic lesions. The spleen was moderately enlarged and weighed 60 gm. The adrenals were of the usual size, but had a striking, deep, hemorrhagic color. On section gross hemorrhagic involvement of the cortex and medulla was present. Histological examination revealed diffuse hemorrhage throughout the entire adrenal substance with beginning necrosis of both the medullary and cortical tissue. Examination of the brain revealed congestion of the vessels of the leptomeninges, but no other gross or histological changes.

Case 2. The history and physical examination of this case are necessarily fragmentary since the child was brought to the accident room in a moribund condition and died within a few minutes after admission. The brief anamnesis was all that could be obtained from a distraught and hysterical parent. This is a white, female child, R. C., aged 2½ years, who became ill quite suddenly during the evening of July 7, 1936. Her illness was characterized by marked prostration, hyperpyrexia and several generalized convulsions. The patient was seen by a physician on the morning of July 8, 1936, at which time she was comatose. The skin of the face, neck, trunk and extremities was covered by a profuse, macular, petechial and purpuric eruption, which, in some places, was confluent. The individual lesions measured up to approximately 5 cm. in diameter. Immediate steps were taken to secure hospitalization, but as stated above, the patient was in a moribund state when first seen in the accident room. Death occurred at 2:00 p.m., July 8, 1936. The duration of illness, as closely as can be determined, was less than 24 hours.

An autopsy was performed one hour after death. External examination revealed a diffuse, macular and, in some places, petechial eruption, involving the face, neck, back, abdomen, chest and the upper and lower extremities. Although only slight rigor mortis was present and only a short time had elapsed since death one was struck by the diffuse cyanotic discoloration of skin, apart from the distinct eruption. The conjunctivae were injected, but presented no petechiae, nor were petechiae seen on any of the serous membranes of the body. There was moderate gaseous distention of the intestinal tract. The thymus was somewhat enlarged, weighing 30 gm., and there was prominence of the mesenteric lymph nodes which appeared somewhat reddened. Lymphoid hyperplasia was, likewise, noted in the Peyer's patches and solitary follicles of the ileum. The lungs, grossly and histologically, revealed evidence of edema and congestion. The heart, liver and kidneys showed no marked lesions aside from a moderate degree of cloudy swelling, compatible with any acute infection. The spleen was enlarged, weighing 65 gm. and histologically showed a typical acute splenic tumor. The adrenals, although of normal size and shape, exhibited a diffuse, deep red, hemorrhagic appearance, which completely obliterated all normal landmarks of cortex and medulla. Histologically there was extensive hemorrhage confined within the limits of the capsule of the adrenal. The densest collection involved the medulla and zona reticularis with apparently secondary involvement of the outer layers of the cortex. There was complete disruption and necrosis of all but a very

small outer shell of adrenal tissue. In addition to fresh blood, collections of blood pigment could be seen scattered throughout the section. A careful search for organisms was made in sections stained by Goodpasture's method, but none were found.

The brain was examined by Dr. James G. Arnold, Jr., who found scattered petechial hemorrhages present, particularly in the region of the ventricular system. One early encephalitic focus was found in the thalamus. There was nothing specific in the findings to suggest a purulent meningitis; they were simply such as might be present in any septicemia.

Blood Culture: postmortem blood culture revealed a pneumococcus, type 1.

Comment

In view of the predominant meningococcal etiology, the infrequency with which these cases are seen is surprising. It appears to us, and to several other observers, notably Rabinowitz, Bamatter and Aegerter, that the thymolymphatic prominence is an important factor in the pathogenesis of this disease. To the 10 reports of thymic enlargement we add, in case 2, additional support in the form of a thymus, weighing 30 gm., in a 2½ year old child. The definite relationship between atrophy, or hypoplasia, of the adrenals and status thymolymphaticus is a well known fact. The assumption that the rarity of these cases is the result of the infrequent coincidence of these two factors can be proved only by further careful observations. Other constitutional and physiological factors have been mentioned, such as the marked vascularity of the adrenals in infants and the increased sensitivity of the suprarenal vessels to vasodilating toxins, but they seem untenable in view of the occurrence of cases in adults.

It is interesting to note, here, that even in cases of definitely proved meningococcal etiology, the leptomeninges have shown only slight involvement in the form of capillary congestion. This, of course, merely supports the well known occurrence of bacteremia preceding the usual manifestations of meningitis.

A hitherto unmentioned pathological finding is noted, also, in case 2, i.e., the occurrence of minute petechial hemorrhages in the white substance of the cerebral hemispheres, especially adjacent to the ventricular system. This, however, is believed to be nonspecific and merely in keeping with the finding of subserosal petechiae in the epicardium, pleura and peritoneum in this and other types of septicemia. It may, however, be of significance as the background for the coma and convulsions often seen in these cases.

The frequency of sterile blood cultures, even in recent reports, is deserving of consideration. Bamatter suggests as possible reasons: Phagocytosis by body cells; antibodies in the serum being carried over into the culture media; the organisms, though few in number, being especially virulent in their effect. Finally, the isolation of other organisms, such as the pneumococcus in one of our cases, necessitates some explanation. One may suggest an ectodermal tropism, similar in a way to that of the meningococcus, on the part of pneumococci.

Summary

1. Two cases of the so-called Waterhouse-Friderichsen syndrome are reported.

2. Review of the literature reveals a total of 64 cases, 70 per cent occurring in children below the age of two years.

3. Twenty-one case reports mentioned bacteriological etiology; 60 per cent were meningococcal in origin. The remaining 40 per cent were due either to *Streptococcus hemolyticus* or the pneumococcus, or were reported sterile after careful examination.

4. The outstanding pathological finding is bilateral adrenal hemorrhage, usually of a massive type.

5. The clinical picture of a rapidly fulminating, septic course, associated with a striking purpura, is considered of sufficient definiteness to warrant consideration of this syndrome as a clinical entity.

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VARIATIONS IN RESPONSE TO THERAPY IN PERNICIOUS ANEMIA*

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Adequate treatment of pernicious anemia should result in the restoration of a normal blood picture and in the disappearance of those symptoms and signs which are not due to irreversible tissue changes. It is necessary to know the amount of potent factor required to bring the erythrocytes to normal and to maintain these cells at such a level. It is also important to determine whether, in spite of apparently adequate therapy, a significant fall in the red blood cell count may occur. If such a fall occurs we should like to know whether it is attended by other evidence of clinical relapse. A study of the records of the patients under active treatment in the Hematology Clinic of the New York Hospital was undertaken to see if information could be obtained which would throw some light upon these problems.

The total series of patients studied numbered 36; of this total, 33 patients had been given treatment for a sufficient period of time to elevate the red blood count to normal, and of these, 32 had been treated in the Clinic for periods of time that permit a satisfactory evaluation of data which might yield information about maintenance conditions. Of the group of 32 patients the average length of the maintenance period was 21 months, the shortest period being five, the longest 50 months. The preparations used in treatment were Lederle Liver Extract (3 c.c. of which were derived from 100 grams of liver), and an unconcentrated extract prepared in the laboratories of the New York Hospital, 10 c.c. of which were derived from 50 grams of liver. The latter preparation was given those patients who could not afford the cost of the commercial preparation. The amount of New York Hospital extract given was shown by experience to produce results comparable to those obtained by the highly refined commercial preparation. These preparations were given by intramuscular injection, the average amount consisting of a total monthly dose of material derived from 300 grams (Lederle) or from 200 grams (New York Hospital). The patients were seen in the Clinic at least once a month when counts were made and the patients questioned and examined. When the red blood cell count fell appreciably or the patient showed some subjective or objective evidence of relapse the amount of material was increased or was supplemented by whole liver or by Lextron.† As these patients were observed on their recurring visits, the impression was gained that the amount of liver given routinely

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† Lextron: (Eli Lilly)-Liver Stomach Concentrate 0.455 gm.; Ammonium Citrate (Green) 0.2 gm. Adsorbed Vitamin B—0.016 gm.

was yielding satisfactory results in most cases, and the counts (both individually and as regards the general trend) seemed up to the normal standards.

A standard for erythrocyte values has been established from numerous studies of normal individuals. Wintrobe [1] has published an analysis of a number of such series from the literature as a result of which the average red blood cell values for men have been placed at 5.4 and for women at 4.8 million erythrocytes per cubic millimeter of blood. In his own series of normals (86 men and 101 women) the normal variation for men was found to lie between 4.9 and 5.98, and for women, between 4.44 and 5.60. In our pernicious anemia patients who were in remission the average count for the entire group of women (19) was 4.5 and for men (13) 4.83. It will be noted that these figures fall below the mean average of the normal group but lie within the limits of normal variation for women and just under the low normal for men. These averages are lowered by inclusion of several cases not satisfactorily controlled. If we consider the mean erythrocyte count of 4.44, given by Wintrobe, as the lower limit of normal variation for women, there were five patients in this group whose average counts lay below this figure, and of the men also five patients whose average remained below the lower figure for men. These patients are presented as cases 1, 21, 31, 23 and 36 (women) and 24, 14, 9, 12 and 25 (men). The lowest average in this group occurred in two women both with counts of 3.9; and of the men, two patients had average counts of 4.3. If these 10 cases are excluded from the series—the 10 records will be later presented in detail—it will be seen that the remaining 23 patients show erythrocyte averages that lie well within the range of normal values and they can be considered well controlled from a hematologic standpoint. Since these patients (70 per cent of the series) gave a satisfactory hematologic response to amounts of active principle which consisted on the average of potent factor derived from 300 grams of liver (Lederle) or from 200 grams (New York Hospital Extract) per month, they may be used for comparison with those subjects whose average counts failed to attain the normal. It will be of interest to compare the amount of active principle given to these latter individuals with the average used for the entire group and to see whether the disease under these presumably unfavorable conditions seemed to be clinically controlled or showed some evidence of activity.

Cases Refractory to Treatment as Demonstrated by Low Red Blood Cell Counts

As previously stated, the average total dose of material per month consisted of substance derived from 300 grams of liver (Lederle) or from 200 grams (New York Hospital). This quantity undoubtedly exceeds the minimum requirement for the average case. Murphy [2] was able to maintain a normal erythrocyte level, of from 4.5 to 5 million or over, with as little as 1 c.c. prepared from 100 grams (Lederle) given at intervals of about 21

days, and Sturgis [3] with an average monthly total quantity of material from 80 grams (preparation not stated). It will be noted, therefore, that although amounts considerably in excess of that usually found effective were given, the average count of these patients fell below the optimal level. A brief summary of this group of "refractory" patients is presented to emphasize the amount of liver extract used, the hematologic response to treatment and the symptomatology as it appeared at the end of the maintenance period arbitrarily chosen for the purpose of the study.

Case 1. A woman, 40 years of age, gave a history of periods of exhaustion, glossitis and diarrhea with intermittent paresthesias of the hands and feet for five years. The erythrocyte count on admission was 1.48 million. The maximum reticulocyte response was 19 per cent on the sixth day, and the erythrocytes reached 4.6 million in the third month of treatment. This level was not held, and an average count of 3.9 million was maintained over a period of 23 months. During this time she received as an average total monthly intake, the material derived from 600 grams (Lederle extract) alternating with that from 200 grams (New York Hospital extract). Her general and neurological symptoms were entirely controlled, and there was no objective evidence of progress of the disease. She experienced periods of nervous irritability and stated that she would fly into a rage with little provocation. She would awaken at night obsessed with fear of she "knew not what."

Comment: Except for periods of emotional instability this patient was free of symptoms.

Case 23. A woman, aged 30 years, with symptoms of vertigo and weakness for two months, showed an erythrocyte count on admission of 2.0 million. A reticulocyte peak of 14.9 per cent occurred on the fourth day of treatment, and an erythrocyte count of 4.5 million was obtained in five weeks with a total dose consisting of the material derived from 500 grams of liver (Lederle extract). The average amount of material given per month over a period of 15 months was that derived from 300 to 600 grams (Lederle extract) and the average erythrocyte level attained during this time was 4.2 million red blood cells. This patient also had exophthalmic goiter for which a subtotal thyroidectomy was done during her treatment for pernicious anemia.

Comment: The general symptoms have disappeared and there has been no evidence of central nervous system involvement.

Case 31. A woman, 47 years of age, complained of weakness, glossitis and flatulence for four or five months. On admission the erythrocyte count was 2.8 million. The reticulocyte response to treatment could not be followed as the patient was ambulatory. The count reached the 4.5 million level after six weeks' treatment during which she received in all the material from 350 grams of liver (New York Hospital extract). During the following year the count averaged 4.0 million while receiving per month material derived from 300 to 600 grams (Lederle extract) alternating with New York Hospital extract derived from 200 grams. This patient has not experienced symptoms in spite of the relatively low count until within the past few weeks, when mild paresthesias were perceived similar to but less noticeable than those that had troubled her some years prior to treatment.

Comment: The disease has been symptomatically controlled until within the past few weeks.

Case 21. A woman, 52 years of age, with an admission count of 3.7 million erythrocytes, was treated for 28 months after the red blood cell count had been stabilized, and during these months the average count was 4.2 million. The monthly intake consisted of the material derived from 300 to 600 grams of liver (Lederle extract) with intervals during which extract from 200 grams (New York Hospital extract) was used. This patient stated that the extreme weakness which she had experienced prior to treatment had entirely disappeared, and the paresthesias which had been severe had improved although they were still present and troublesome. Vibration sense on admission was reduced in both upper and lower extremities and was unchanged after a two year period of treatment. There was some loss of joint sense, and the heel to knee test was poorly performed. There was some impairment of cutaneous sensibility over the lateral halves of both legs and much mental depression and irritability. None of these features was altered during the maintenance period although the extreme mental confusion and lack of orientation present at the time of her admission to the hospital cleared following a few weeks of treatment.

Comment: This must be considered an unsatisfactory result, both as regards subjective and some objective evidences of the disease. The blood reached 4.5 million erythrocytes at one time. Then the therapy was changed to ventriculin. The immediate response was good, but after return to liver extract the erythrocyte count dropped and remained below the desired level.

Case 36. A woman, aged 41, had been treated six months previously in the hospital, but because the count could not be maintained, she was readmitted with a count of 2.3 red blood cells. The maximum reticulocyte response of 17 per cent occurred on the eighth day, but the count never reached 4.5 million. Material from 3500 grams of liver was given during her month's stay in the hospital. During the 15 months following she has received amounts of material ranging from that derived from 200 grams (New York Hospital extract) to that from 400 grams (Lederle extract) within four week intervals. The erythrocyte level has averaged 3.9 million. With this relatively low level there have been no outspoken signs of the disease, and she has never shown evidence of central nervous system involvement. However, she has not felt in perfect health and has continued to tire easily.

Comment: Although this patient was given somewhat more liver than the average patient, undoubtedly in view of her general symptoms of fatigue a larger amount should be given in an attempt to elevate the blood to a higher level. This patient was mentally depressed and undernourished. Whether these conditions had an indirect effect upon the production of erythrocytes is a matter for conjecture.

Case 24. A man, aged 36 years, was admitted with an initial count of 2.8 million red blood cells. The reticulocyte response was not obtained as the patient was ambulatory. The erythrocyte count rose slowly over a period of five months to a level of 4.5 million. This count was not maintained, however, and he continued to complain of flatulence and of vague gastrointestinal symptoms with much mental depression. The average count over a period of nine months was 4.3 million on a monthly total intake consisting of the material from 300 grams of liver (Lederle extract). The glossitis, which had been present prior to treatment, disappeared. The central nervous system remained objectively negative, and there were never any paresthesias. Following a change in his fortunes the gastrointestinal symptoms disappeared, and it

is possible that they were in part of functional origin, although the Graham-Cole roentgenogram of his gall-bladder showed the presence of adhesions.

Comment: Although this patient's blood count remained at a relatively low level, he obtained satisfactory symptomatic relief, and there was no apparent progress of his disease.

Case 14. A man, aged 66, was under treatment for 15 months. His initial count was 1.4 million erythrocytes and the reticulocyte peak, occurring on the sixth day, was 30 per cent. There was a slow rise over a five month period during which he received material from 550 grams of liver (New York Hospital extract) in the first month, and in subsequent months that from 600 to 1200 grams (Lederle extract). Following the use of the Lederle extract from 1200 grams the erythrocyte count reached a level of 4.7 million, which, however, was not maintained with subsequent monthly doses of Lederle extract from 300 grams. The average count over a 12 month period was 4.3 million. In spite of this relatively low level he became symptom free at an early stage in his treatment, regained strength rapidly, and the diarrhea which had greatly troubled him disappeared. The paresthesias present intermittently for five years cleared entirely except on crossing one knee over the other when the pendent extremity became numb to a greater degree than he considered normal. No change, however, was observed in the hyperactive reflexes.

Comment: This case is of interest because of the large amounts of liver necessary to raise the count temporarily to within normal limits, at which level it was not maintained with average amounts of liver. There was no evidence of progression of the disease and the patient was practically symptom free.

Case 10. A man, aged 60 years, stated that he had been troubled with weakness, exhaustion and paresthesias to a greater or lesser extent for three years. His erythrocyte count on admission was 1.9 million. The reticulocyte response rose to 38 per cent on the twelfth day, and in 11 weeks his erythrocyte count had risen to 4.5 million with the use of material from 600 grams of liver (Lederle extract). During the 32 months of treatment to date he received as an average monthly dose the material from 300 grams of liver (Lederle extract) alternating with New York Hospital extract from 200 grams of liver, and the level of his erythrocytes during this period was 4.6 million. The general symptoms were completely relieved, but the paresthesias persisted over the two year period of treatment and were described as a sensation of hot water on his finger tips and a band-like constriction around his knees. Vibration sense was reduced below the twelfth dorsal segment and absent over the knees, ankles and toes. Cutaneous sensibility was impaired below the twelfth dorsal segment. There was no improvement in the symptoms of central nervous system involvement during treatment, but, on the other hand, there was no progression of objective signs.

Comment: An apparent arrest of moderately advanced subacute combined sclerosis with only fair hematologic response to treatment.

Case 12. A man, aged 84, gave a history of symptoms for nine months prior to his admission. During the first year of treatment his count averaged 4.1 million while being given the material derived from 500 to 600 grams of liver (Lederle extract) at monthly intervals; during the second year, the count averaged 3.6 million on extract from 600 grams of liver (Lederle extract) once a month; during the third and fourth years 4.4 and 4.6 million on extract from 600 to 800 grams of liver (Lederle) once a month. As supplementary treatment he was given six Lextron

capsules daily as well as whole liver in amounts approximating 230 grams daily. Although the amount of liver administered was large (at times he received extract from 300 grams twice weekly) the count was at no time above 5,000,000 red blood cells and the average for the total maintenance period falls below the normal as noted. His general response to this treatment was very satisfactory and his strength and sense of well-being were remarkable considering his advanced age. Incapacity from involvement of the central nervous system, however, progressed slowly; there was a gradual and progressive loss of vibration sense in the lower extremities, the paresthesias of the hands and the band sensation of the legs seemed at times more troublesome, the ataxia became more marked, the Romberg was persistently positive and the finer movements of the hands were performed with difficulty. The advance of these changes was so slow that it was scarcely perceptible to the patient who was able, in spite of his age, to carry on an active life as an actor in a federal project.

Comment: It was impossible to control the progress of the disease in this aged man in spite of exceptionally large amounts of active principle.

Case 25. A man, aged 55, gave a history of symptoms referable to pernicious anemia for a year and a half prior to admission. The initial count was 3.2 million. The maximum reticulocyte count of 6.7 per cent occurred on the seventh day of treatment. There was a slow rise over a period of five months during which a total dosage consisting of the material derived from 3550 grams of liver was administered, 550 grams of which were extracted by the New York Hospital method and the remainder by Lederle. The average count of 4.6 million was maintained over a period of six months by the use of material from 600 grams of liver (Lederle extract) monthly, supplemented by a daily oral intake of 230 grams of whole liver and six Lextron capsules. During this time he became practically symptom free and stated with enthusiasm that he felt better than in many years. Paresthesias of a constrictive nature about the waist and thighs and numbness of his fingers disappeared within six months after his blood had reached the 4.5 million level, except as he repeatedly stated, when he smoked cigarettes, following which the paresthesias, especially in the legs, reappeared. Vibration sense was diminished in the lower extremities and did not return. The central nervous system was otherwise objectively negative.

Comment: This case may be considered controlled although the erythrocytes have remained below the desired level.

Of these 10 patients whose erythrocyte counts did not measure up to the normal standard with therapy which is usually adequate, eight have apparently been fully controlled as far as symptoms and signs are concerned. In two the disease showed some evidence of activity. One of these latter showed slight amelioration of symptoms and the other evinced a slow progression of central nervous system changes. In this last case (case 12) it is possible that advanced age may have played a part in the resistance to treatment. As for the former (case 21) there was no objective evidence of advancing signs of the disease although the symptoms were only slightly improved by treatment. In commenting on case 21, it is only fair to point out that the same condition may exist in patients whose blood counts are at or above normal levels, as in case 29 which will be later presented in detail. This patient (case 29) had a normal red blood cell count and hemoglobin, although he had never received liver prior to admission. The symptoms likewise failed to respond to massive liver therapy although there was no ob-

jective evidence of progression. As regards the amount of liver given this refractory group of patients, it will be noted that none of these patients received less than the average amount of liver which served to maintain the blood of 70 per cent of the series at a normal level (Lederle extract from 300 grams of liver or New York Hospital extract from 200 grams of liver monthly); all of the women and three of the men received approximately twice the average amount and two patients received supplementary oral liver.

In contrast to the relatively large amount of active principle given these "refractory" patients, an occasional patient proved to be satisfactorily controlled from a hematologic as well as from a clinical standpoint on a much smaller amount of liver. The two cases which follow illustrate (a) the ease with which one patient was maintained on a small amount of liver (Lederle extract from 150 grams of liver) monthly and (b) in the second case, progressive improvement in the blood count on a constant amount of liver (Lederle extract from 300 grams, or New York Hospital extract from 100 grams) given over a period of three years. In the first case, since it was exceptional to obtain maintenance of a satisfactory count on such a small amount of material, the question arose as to whether the treatment might have coincided with a spontaneous remission. However, since the dose was not altered during a year's time and since Murphy obtained satisfactory results with equally small amounts of material it probably represents actual maintenance conditions.

Case 5. A woman, aged 55, gave a history of marked weakness, some dyspnea, sore tongue and periods of diarrhea. Paresthesias had not been present. On admission her erythrocyte count was 1.08 million. The maximum reticulocyte response of 33 per cent occurred on the eighth day, and the erythrocytes rose to 4.5 million in 13 weeks on a total intake consisting of the material from 2500 grams (New York Hospital extract from 1300 and Lederle extract from 1200). Thereafter her blood was maintained for one year to date at an average of 4.9 million red blood cells on material from 150 grams of liver (Lederle extract) at monthly intervals. Her symptoms cleared entirely and there were no objective signs of the disease.

Of interest also is the second case because the blood displayed an increasing rise of the erythrocyte level during the period of study (approximately three years) on a constant amount of liver, not exceeding the average monthly dose given the entire group (Lederle extract from 300 grams of liver). It would seem that a gradual storage of active principle may occur which yields a maximal hematopoietic effect only after some time has elapsed.

Case 4. A man, aged 59, sought medical attention because of extreme weakness and exhaustion. He had noticed transient paresthesias and stated that his sense of taste had become impaired—that all food "tastes and smells like rubber." His red blood cells on admission numbered 1.82 million, and the maximum reticulocyte response of 34 per cent occurred on the tenth day. The count rose to 5.1 million on material from 600 grams of liver (Lederle extract) in six weeks but thereafter dropped and remained at an average level of 4.5 million for six months on material from 300 grams of liver (Lederle extract) monthly. During the second six months the aver-

age count rose to 4.7 million, the following 10 months to 4.9 and during the 10 months to date it averaged 5.2 million. For a period of 20 months New York Hospital liver extract (derived from 100 grams of liver) was given at monthly intervals, during which time as well as during the time that the Lederle extract was given there was an approximate monthly increase of 30,000 erythrocytes.

The patient is entirely symptom free. His general strength is excellent and he states that his sense of smell has returned to normal. The paresthesias have practically disappeared. However, vibration sense remains impaired below the twelfth dorsal segment.

Time Required for the Erythrocyte Count to Reach 4,500,000 and Amounts of Liver Used

The group of 33 cases was analyzed to determine the length of time required and the amount of material used to bring the count to 4,500,000 red blood cells. Since some differences were observed that could not be entirely explained by the height of the initial count, an attempt was made to determine other factors, as for example the duration of the disease prior to treatment, which might be operating to delay the response to treatment. The estimated duration of the disease prior to treatment as dated from the first symptom noticed by the patient may be unreliable. In many instances the development of symptoms is so gradual that they may not be noticed until some unrelated event, such as an acute infectious disease, brings the symptoms to the patient's consciousness. Many patients, however, do offer a definite opinion as to when their symptoms began, and an attempt was made to correlate this with the time required to bring the count to normal. Some correlation will be noted. Of the 33 cases, 15 reached the 4.5 million level in two months or less. The average total amount of liver extract given was that derived from 670 grams (combined New York Hospital and Lederle extracts). The average initial count was 2.6 million erythrocytes. The duration of symptoms prior to treatment averaged 13.1 months. Of a second group requiring more than two but under three months to reach this level, there were 11 patients with an average initial count of 1.9 million. The average amount of material used in this group was that derived from 1072 grams (combined New York Hospital and Lederle extracts). The approximate duration of symptoms averaged 23.1 months.

A third group emerged from this analysis which was of considerable interest. This consisted of a number of patients who required more than three months for the erythrocyte count to reach the 4.5 million level. Many observers regard it as exceedingly unusual for the blood to fail to reach 5,000,000 within eight weeks, even with relatively small amounts of liver extract. Murphy found that 1 c.c. prepared from 100 grams of liver weekly was sufficient to raise the blood to the 5,000,000 level in eight weeks or less. In our group there were seven patients who required over three months to reach a count of 4,500,000 and to whom a minimum consisting of extract from 1600 grams and a maximum of extract from 6,600 grams of liver were

given. In these patients the average initial count was 2.9 million, and the slow rise is the more surprising in view of this high initial count. One patient in particular may be cited (case 36), who was given a total consisting of extract from 6,600 grams but whose count did not rise above 4.1 million in five months. In spite of this atypical response the diagnosis of pernicious anemia was retained as all other causes for her anemia had been excluded. Because of the special interest in this group of cases the details of these cases are summarized in the table. Other features in the clinical history or examination that were in any way unusual are enumerated in the column under the caption " remarks," although there is no experimental evidence that the rate of hematopoiesis is influenced by any of the factors mentioned.

TABLE I

Cases Refractory to Treatment
(More than three months required for red blood cells to reach 4.5 million)

Case	Age	Duration of Symptoms (Months)	Initial Count	Time to reach 4.5m (Months)	Therapy (total grams)*	Remarks
12	84	9	3.6	9	5400	Senility
14	66	72	1.4	5	3860	Senility Frequent relapse in six years No C.N.S. involvement
24	36	12	2.8	5	2000	Marked depression
25	55	18	3.2	5	3000	Chronic sinusitis
27	68	72	3.9	4	1600	Insufficient liver (?) Senility Malnutrition Long history
31	52	1—	3.7	4	900	Insufficient liver (?)
36	41	1	2.3	5 to 4.1m	6600	Marked depression (situational)

* Total of grams of liver, the extract from which (Lederle extract and New York Hospital extract) was administered.

It will be noted in the summary of the entire group that less than half of the patients showed a rise of erythrocytes to the 4.5 million level in less than two months. This result does not correspond with Murphy's experience, since all but two of his patients reached the 4.5 level in two months or less, and none failed to reach the 5 million level on amounts of extract between that derived from 500 to that from 1500 grams of liver (Lederle). The amount of liver extract used by our patients whose blood reached the 4.5 million level within two months was derived from 200 to 1500 grams of liver, but corresponding amounts failed to elevate the count of the remaining 18 of the 33 cases. Murphy states, " Failure of the blood to reach 5,000,000 or more within about eight weeks or less was usually due either to failure on the part of the patient to appear regularly for treatment or for blood counts at the proper intervals." Our patients reported for counts at weekly, biweekly or at the latest, monthly intervals so that it does not seem likely that

the erythrocyte rise to the expected point escaped detection, and in those with a slow rise, later counts served as a control for the earlier counts. All patients had been thoroughly investigated, the majority as pavilion patients in the hospital, before the diagnosis of pernicious anemia was accepted and active therapy instituted.

Response of Symptoms Referable to the Involvement of the Nervous System

The most serious and persistent symptoms encountered in the routine care of the clinic patient with pernicious anemia are those that result from combined system disease or from peripheral neuritis. These may be the first to appear and often prove the most resistant to treatment. Neuropathologists are not in agreement as to whether a true peripheral neuritis exists as a basis for the paresthesias, although when these symptoms are mild and transient and tend to disappear with treatment it is customary to attribute them to a neuritis of the deficiency type. When, on the other hand, they persist in spite of intensive treatment and a normal blood picture, or slowly increase in severity, one cannot escape the conviction that they have their origin in a progressive involvement of the cord. Woltman,[4] who has made an intensive study of the brain changes associated with pernicious anemia, in a personal communication has commented as follows on this point. " You have raised a question that has bothered me a great deal also, namely the source of the paresthesias. There is no question about the degeneration in the peripheral nerves described by Hamilton and Nixon [5] but I am by no means certain that they always account for all the paresthesias these patients have. The progress of paresthesias associated with pernicious anemia in an upward direction until the lower portion of the trunk is included certainly suggests that they may also have their origin in the spinal cord as does the not infrequent failure to disappear more completely than they sometimes do on adequate treatment. The paresthesias often do disappear entirely, as might be expected in cases of degeneration of the peripheral nerves or where the spinal cord has not yet been too severely involved. That changes in the spinal cord may recede in some cases is proved by the occasional change of a positive Babinski sign to a negative one."

The subjective complaints from the paresthesias often seem out of proportion to the objective signs of cord involvement which may be so slight as to escape detection except by the most careful examination. For conclusive objective evidence not only of involvement, but especially as regards progression or regression, observations should be made at frequent intervals by the same examiner, as emphasized by Grinker and Kandel.[6] Even under properly controlled conditions an evaluation of the findings is often extremely difficult. Vibration sense, two point discrimination, cutaneous sensibility are often unreliable in details, varying with the subjective interpretation of the patient not only from one examination to another but often

during the same examination. Objective signs offer more reliable criteria, and more significance may be attributed to such signs as a change from an ataxic to a normal gait, a decrease in sphincter disturbance, the disappearance of spasticity or a return to the normal of a Babinski reflex or of the Romberg sign.

Since the paresthesias often constitute the most troublesome symptoms and may persist after the general symptoms—the extreme exhaustion, the glossitis, the gastrointestinal manifestations,—have disappeared, they stand out in the patient's mind as an indication of whether or not the treatment is proving successful. Such symptoms consist not only of the familiar numbness and tingling but of various other abnormal sensations, among the most common of which is constriction, described as a band sensation around the body or the thighs or legs, occasionally around the head. Such expressions as " my head feels tight as a drum," " my chest seems in a vice," " legs feel as if they were bound and would burst " are common. An abnormal temperature sensation " as if my hands were in hot water " or " my feet feel as if I were walking on ice although they are not really cold " often is described. Extreme hyperesthesia occurs—" if the cat brushes against my legs it causes acute pain." Difficulty in walking may result from spasticity or from an altered position sense—" I am not sure where my feet are when I take a step." Defective sense of position gives rise also to such expressions as " I lose my legs in bed," " cannot sew because I do not feel the needle or know where it is going." Altered cutaneous sensibility in the feet is not uncommon, so that the patient feels that he is " walking on cotton," or " standing on a rubber ball," or the " hands feel as if they were stuffed." Occasionally actual pain is experienced, often in the legs or back. One patient described acute pain shooting from the soles of the feet up into the calves of the legs. Because of the severity of these symptoms various measures have been employed, but for the most part with little success. They have ranged from the use of large amounts of vitamins to various physical therapeutic measures. In one patient who complained of severe pain in the back roentgen-ray therapy was utilized with the hope that this method of treatment which is occasionally effective in certain types of intractable nerve pain might prove helpful in relieving the symptoms. No appreciable improvement was experienced. In those patients showing mild cerebral manifestations, such as depression, apprehension and irritability, a sedative often was beneficial. As a rule, marked cerebral disturbances, such as confusion, memory defects, paranoid tendencies or delusions, disappeared during the initial treatment.

Of the total series of 36 patients in this group, eight never experienced subjective symptoms other than transient paresthesias, four were entirely relieved of such symptoms which varied in degree, 15 were considerably improved although not entirely free, in five the symptoms were unchanged and in three they became definitely worse. In one, although the paresthesias

were relieved, shooting pains had developed in the legs. As regards objective signs of the disease, as far as they could be determined by the clinic records, only one showed definite progression of the disease (a man aged 84 years); 17 were unchanged; in eight there was apparent improvement; and in 10 objective signs of involvement of the central nervous system had never been detected.

Not infrequently one encounters the report of subacute combined sclerosis not associated with the blood picture of pernicious anemia but apparently due to the same cause. If the etiologic factor is identical with that which produces the anemia, it is interesting to note that the severity of the central nervous system disease does not necessarily parallel the severity of the anemia. Nevertheless it is assumed that amounts of active principle which will elevate the blood to 5,000,000 or above will prevent the progression of central nervous system changes. When, however, the blood count has never been reduced, the count obviously cannot serve as an index of adequate treatment; and sufficient active principle is given, or more than necessary, to maintain the count at a high normal level, because of the empirical observation that if the blood is so maintained the central nervous system disease is held in control. Castle and Minot [7] summarize our lack of knowledge of this phase of the disease as follows, "Until the hematopoietic principle of liver is isolated it will be impossible to find by therapeutic test whether it is also specific for the neural disturbance, or whether multiple factors, either intrinsic or extrinsic, are involved." The following case affords some evidence that progression of combined sclerosis may be held in abeyance by the administration of active principle. This patient has been under observation and treatment for three years. Although he has not been relieved of his symptoms—indeed he states that the paresthesias have become more severe—there has been no objective evidence of progression and the return to normal of the ankle jerks and of the Babinski reflex would indicate that some actual improvement had occurred.

Case 29. A man, aged 63, for a year and a half prior to admission had noticed great weakness, diminished power in his lower extremities and marked paresthesias of his hands and feet as well as a sense of constriction in his thighs. He dated the onset of his symptoms from an acute respiratory infection. Examination revealed markedly increased tendon reflexes with a positive Babinski. Position sense was very faulty and the Romberg sign was positive. Ataxia was marked, and he was unable to walk because of this and as a result of weakness. Vibration sense was greatly diminished in his lower extremities. He had never received liver or any other treatment. His hemoglobin estimation was 11.6 grams; red blood cells numbered 4,800,000; reticulocytes 1.2 per cent. The hematocrit reading was 46 vol. per cent, and the volume index 1.1. There were some macrocytosis and anisocytosis. No free hydrochloric acid was demonstrated in his gastric contents with histamine stimulation. The spinal fluid did not impress the neurologist who saw him as of diagnostic significance, although the protein content was slightly increased and the colloidal gold curve appeared as 2222111111. There were 245 c.c. of residual urine, and the renal functional tests yielded normal values. The diagnosis was that of subacute combined sclerosis, and liver extract was given by intramuscular injection.

His general condition rapidly improved so that when he left the hospital he was able to walk without assistance. He has continued to feel very well generally but his paresthesias have persisted as well as the spastic gait and some degree of ataxia. He has received material from 600 grams of liver (Lederle extract) at monthly intervals as well as six Lextron capsules and whole liver daily (approximately 230 grams). Large amounts of vitamin B have been included in his diet. His erythrocytes over a period of 19 months have been maintained at an average count of 5,000,000. The sense of tightness, coldness and numbness of his hands has persisted, but a recent neurological examination, although unchanged in other respects, reveals that his Babinski reflex has returned to the plantar response and that the ankle jerk is of normal amplitude.

Discussion

This study of the response of 32 patients with pernicious anemia to definite amounts of potent factor brings out several points of interest. It was thought on the basis of the satisfactory response of the majority of patients, as well as on the basis of the experience of other workers, that the average amount of material used (Lederle extract of 300 grams of liver or New York Hospital extract of 200 grams of liver per month) was ample, and indeed, in excess of what was required for adequate maintenance of the blood at normal erythrocyte levels. It was a surprise, therefore, to find that approximately one-third of the patients of this small series showed average red blood cell counts below the standard of normal. The majority of these "refractory" cases (eight of the ten) were given approximately twice the amount of material received by the other 22 patients who showed a "normal" response (an average of Lederle extract from 600 grams as against that from 300 grams of liver per month) as well as in several instances, supplementary liver by mouth in an amount, in itself, often found sufficient to maintain the average patient. It must therefore be concluded, since this unequal response occurs in a fairly large number of patients, that each patient with pernicious anemia must be managed as a separate problem and the dose individualized on the basis of the trend of the erythrocyte count averaged over stated intervals of time. The fact that the disease in eight of these ten "refractory" patients with low average erythrocyte values was controlled from the standpoint of signs and symptoms would make it appear that for some individuals a slightly substandard level of the erythrocyte count under treatment is not inconsistent with a satisfactory state of health. Nevertheless, the low level of the erythrocytes should be recognized and every effort made to elevate and stabilize the blood at a higher level. The possibility of relapse in these patients with severe damage to the nervous system, even when apparently under control, should never be forgotten. In our series, fortunately, no such serious relapse has occurred.

A second point of interest developing from the study consisted in the time required to bring the initial count to the minimum normal level. Although the majority of the group reached this minimum level within three months, and 15 within two months, in general the time required was in

excess of that reported by Murphy, who used corresponding amounts of material. In seven patients of our series even longer periods of time than three months elapsed before the red blood cells reached 4.5 million. Although, again, the amount of material was the same or more than that given the majority of the group and the initial count in several instances was not low, the blood of these individuals rose more slowly that it did in other instances where the initial count was considerably lower. These patients had been carefully studied and the diagnosis satisfactorily established; in several the pernicious anemia had been recognized and treated some years previously, but they were in relapse when the treatment which forms the basis for this study was begun. No satisfactory explanation can be offered for the atypical response of these patients, but many of them were additionally handicapped by some outstanding condition other than the pernicious anemia, as for example, a continuous depressive state arising from an unfortunate domestic or financial situation or by malnutrition or senility. Whether such conditions do actually influence the rate of hematopoiesis is a matter for conjecture. Whatever the cause for these retarded responses, it would seem that no unqualified prediction can be made as to the length of time necessary to bring the count to normal on the basis of the level of the initial count or as estimated by the response of the average patient.

It would seem also that the effect of treatment upon the neurological aspects of the disease cannot be predicted. Senility, in one case in this series, in the presence of a fairly well elevated and sustained erythrocyte level, seemed responsible for the unsatisfactory result in controlling the central nervous system disease. The extent of central nervous system involvement may not parallel the red blood cell count. Several patients who had had repeated hematologic relapses did not show evidence of neural disturbance, whereas the most advanced case of combined sclerosis in the series had never been anemic. The difficulty of following the course of the combined system disease makes it imperative that careful, detailed and frequent neurological examinations be made and that maximal amounts of potent material be given these patients regardless of the height of the red blood cell count.

Finally, this study demonstrates that although the more concentrated material is more satisfactory for use because of its greater freedom from unpleasant reactions, it is not equal in potency to the unrefined preparation. Whereas material from 100 or 200 grams of liver represented in the unrefined preparation controlled the average case, an amount of concentrated preparation derived from 300 grams of liver was required for equally good results. Potent factor undoubtedly is lost in refining and in concentrating the material, and the amount available in the various preparations cannot, therefore, be measured accurately by the weight in grams from which the material was derived. In view of this variation in potency which depends upon technical methods of extraction and refinement, it is advisable to record not only the weight in grams represented by the preparation, but the specific brand employed.

Conclusions

1. The average red blood cell count of 32 patients with pernicious anemia was 4.5 million for women and 4.83 million for men after hematopoiesis had been stabilized by treatment. The average amount of material used was Lederle extract derived from 300 grams of liver or New York Hospital extract from 200 grams per month.

2. Ten of the 32 patients showed erythrocyte values below normal standards although active principle much in excess of what was adequate to control the average case was given. However, in eight of these ten cases the disease appeared to be clinically controlled.

3. The length of time required to bring the blood count to 4,500,000 was two months or less in 15 patients and between two and three months in 11. The initial count of those requiring two months or less was 2.6 million; of those requiring between two and three months the initial count was 1.9 million. Seven patients required more than three months to bring their count to normal. The poor general condition of these patients, due to various causes other than pernicious anemia, may have had a depressing effect upon the rate of hematopoiesis.

4. Of the total series of 36 patients only eight had never experienced symptoms of peripheral or central nervous system involvement. Following treatment, of 28 who experienced symptoms, four were entirely relieved, 15 were improved, in five there was no change and in three they became worse. In one the result was indeterminate. It will be seen, therefore, that although the majority of patients are benefited by treatment, no absolute prediction as to relief of symptoms can be made.

5. In spite of intensive treatment one patient showed progression of objective signs of central nervous system involvement. In 17 the signs were unchanged; in eight there was apparent improvement. In 10 patients there were no objective signs of neural disturbance.

6. Although patients may be free of signs and symptoms of pernicious anemia with average counts slightly below the normal, the fact that two patients with such levels showed evidence of beginning relapse indicates that a continued effort should be made to elevate and maintain the blood at a high level.

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ARACHNODACTYLY AND STATUS DYSRAPHICUS; A REVIEW *

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Part I. Arachnodactyly

The clinical picture of arachnodactyly as described by Marfan is so characteristic that one having it in mind could hardly fail to recognize it. Since the original description little has been added; there have, however, been an increasing number of case reports in recent years. We have been able to find but 13 reports of the disease in the English-speaking literature since 1903 and of these only three came from this country. It becomes apparent then that the condition is relatively unknown on this continent and it is equally true that the diagnosis will be made more often as our familiarity with it increases. Lloyd [1] gave in his recent article such an excellent résumé of the subject that this paper would hardly be justified were it not for the fact that an entirely new significance has attached itself to the condition through a new idea of Passow. This will be reviewed in the second half of this paper.

The essential feature of arachnodactyly is the striking length and slenderness of the extremities, especially of the hands and feet. To this is added the invariable accompaniment of other congenital defects such as cardiac or pulmonary anomalies, webbed fingers, highly arched palate, muscular dystrophy, spurring of the os calcis, and ectopia lentis. The condition apparently has its onset during intra-uterine life since in the majority of cases the typical thinness of the extremities is noted at birth. There does not seem to be a predilection for any particular sex. Weve [2] in 1931 found that of 82 cases reported to that time, 40 were females and 42 males. Most of the patients (about 50 per cent) are below the age of ten. However, Weve found 20 cases between 10 and 20 years of age. Two of Weve's cases were 40 and 62 years old, respectively, and Ormond's case was forty-seven.

The first description of the syndrome came in 1896 by Marfan [3] who gave it the name "delichostenomelia." He also used the exceedingly apt term "Spider Feet" because of the likeness of the narrow fingers and toes to spider legs. In 1902 Mercy and Babonneix [4] suggested the name "hyperchondroplasia." Achard [5] called the condition "arachnodactyly" and this term has been accorded more frequent use than the others. Weve felt that all these terms expressed only part of the clinical picture or were prejudiced concerning the underlying pathology. He believed "congenital mesodermal dystrophy" a better term but preferred simply to use "Marfan's syndrome."

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Case Reports

Case 1. R. M., a boy, aged six, had poor vision all his life. It was impossible to ascertain the vision in the usual way, due to his poor mentality, but it was evident from the way he used his eyes that he had very little sight. He was a tall slender child. The extremities were slender and the fingers and toes unusually long. There was webbing of the fingers. The muscles were poorly developed and this added to his appearance of thinness. The skull was dolichocephalic with prominent forehead and flattened occiput. The palate was highly arched. There was moderate kyphosis and moderate left scoliosis of the thoracic spine. The scapulae were winged. The thorax was of the asthenic type, flat and narrow. There was no deformity of the thorax, no acrocyanosis, no deformity of the feet or spurring of the os calcis. The nipples were symmetrical.

There was a dislocation of the lens in each eye downward and to the left. The pupil was small but reacted promptly to light and dilated well with mydriatics. The lenses were hazy and dotted with punctate opacities. The iris, O.U., was tremulous. Coöperation was very poor but we were able to determine retinoscopically that the eyes were approximately 20 diopters hyperopic. At later examinations we noted that the lenses seemed to change position rather easily. There was no indication of heterochromia or Horner's syndrome. The boy was obviously defective mentally and a psychological examination was made by Dr. M. B. Weiner who concluded that there was cerebral maldevelopment. A considerable improvement in the boy's mental reactions was noted after he had worn 15.00 D spheres before each eye for several weeks.

Case 2. G. K., a boy, aged five years, had always held things close to his eyes in order to see them. This patient was seen only once and our examination was incomplete. We are indebted to Dr. D. M. Stiefel for additional data. His complaint was that he tired easily when standing or walking, and that he had poor vision. He complained also of his legs and feet hurting. The most striking feature was the general hypotonicity of his skeletal musculature. This was exemplified by his great weakness and by the hyperextensibility of his wrists, ankles, elbows and hips. His hands and feet were unusually long and slender, and the fingers and toes were thin and tapering. The external ears showed a deficiency of the cartilage and deformity of the helix. The palate was highly arched. The skull was dolichocephalic. The scapulae were winged and the spine showed moderate scoliosis. There was a definite lack of subcutaneous fat which added to his wasted appearance. According to Dr. Stiefel the boy had a congenital heart defect.

Examination of the eyes showed bilateral iridodonesis. The pupils were small and responded poorly to homatropine. The lens on each side was luxated temporally. The fundus details could not be seen, and retinoscopy was difficult. Vision was 20/200 in each eye and was not improved with lenses, although the retinoscopy suggested a high hyperopia. The patient was not seen again and no further examination was made.

Case 3. Mrs. F. B., a woman aged 37 years, had high myopia and dislocation of the lens in each eye, and detachment of the retina in the left eye. The patient was an exceptionally thin tall woman and her arms and legs were unusually long and slender, a fact which had been noticed shortly after her birth. The slenderness of the limbs was most marked distally and the fingers were typically "spider fingers" of the type seen in arachnodactyly. The phalanges were most involved. The skull was long and narrow. The hard palate was highly arched. The thorax was narrow, flat, and tapered toward the waist. There were no deformities. The scapulae were winged markedly. There was slight scoliosis of the dorsal and lumbar spine. The breasts were symmetrical and equal in size. Auscultation revealed a loud blowing systolic murmur at the cardiac apex. Her feet were unusually long and she stated when she bought shoes the salesmen always mentioned the fact. There was no spurring of the

os calcis. There was a noticeable lack of subcutaneous fat over the body. The hands and feet were moist and warm. All the joints showed hyperflexibility. Roentgenograms of the hands and feet showed normal bone structure but the phalanges and metacarpals and metatarsals were slender and tapering. The patient's father was not seen but he was said to be very tall and thin with long hands and feet. He was said to have become blind " from glaucoma."

Vision O.U. equalled perception of light. Projection of light was excellent with the right eye but very poor especially in the lower field, with the left eye. In the right eye the anterior chamber was deep and the iris tremulous. The pupil reacted well to light but did not respond well to a mydriatic. The lens was densely white and opaque, and trembled with movement of the eye. The direction of its dislocation was not ascertained since the pupil did not dilate well and a slit lamp examination could not be made. In the left eye the anterior chamber was deep and there was iridodonesis. The pupillary reaction was normal but its response to mydriatics was sluggish. The pupil was aphakic. The lens could be seen with the ophthalmoscope, lying in the vitreous below. The retina above was detached, the detachment involving the upper half of the fundus and extending downward covering the macula. There was no heterochromia or Horner's syndrome in either eye.

Case 4. E. T., a boy of 20, had poor vision all his life, with $+8.00+3.00\times120$ V.O.D. $=6/30$, $+6.00+3.00\times90$ V.O.S. $=6/30$ but could not be improved. He showed bilateral dislocation of the lens, iridodonesis, and sluggish response of the pupils to mydriatics. The lens O.D. became dislocated into the anterior chamber and was removed but vision could still not be improved.

The fingers were long, thin and tapering and the arms were long. The span of his extended arms was four inches greater than his body length. The palate was highly arched. He showed no deformity of the thorax and there was no evidence of any heart lesion. The feet were long with long toes. No spurring of the os calcis. The muscles were well developed.

Shortly after the lens O.D. was removed he suffered a skull fracture in an automobile accident. At this time he developed detachment of the retina O.D. Since that time he has been operated on several times elsewhere for meningeal adhesions, to relieve epileptic attacks.

Case 5. L. T., a girl nine years old, sister of case 4, showed a bilateral dislocation of the lens downward. The pupils did not dilate widely after instillation of homatropine. There was iridodonesis O.U. The fundi were negative. Vision O.D. = CF at 6 ft. and O.S. = CF at 3 ft. $A+10.00\ D^s$ each eye brought the vision up to 20/200 but it could not be further improved. The hands were rather gracile with tapering fingers. The feet were not unusually large. The palate was rather highly arched. The scapulae were winged and she showed an indentation near the lower part of the sternum suggestive of funnel chest. There was slight scoliosis. No evidence of heart disease, no deformities of the ears, no spurring of the calcaneus. The muscular system was not abnormal.

The mother of these two patients also had subluxation of the lens but showed no other evidence of the disease.

Relatively few cases of arachnodactyly were reported in the early years following the first description. Rietschel [6] in 1917 found nine cases in the literature and in 1928 Carrau [7] found but twenty. Weve added 23 of his own cases in 1931 to the 60 previously reported. Twenty-two additional cases have appeared since 1931. Arachnodactyly is definitely familial. In the early cases this was not noted but more recently it has been found that practically all patients have other members of the family exhibiting char-

acteristics of the disease. Lloyd [1] reported five cases in a family of six, King [8] described three cases in one family, and Viallefont and Temple [9] presented four members of one family with the condition. Weve's 23 cases belonged to six different families, in each of which more than one member was involved.

The etiology is not known. Some authors believe it is an endocrine disorder, placing greatest importance on the pituitary gland. Many of the essentials of the condition such as the long jaw, the long limbs, the hypertrophied ears, lend support to this idea, but the thinness of the bones is in direct opposition to it. One author expressed the opinion that dysfunction of the pituitary caused acromegaly in adults, gigantism in infants, and arachnodactyly in fetuses. Young discredits the pituitary theory since with few exceptions the onset takes place in intra-uterine life. It has been stated that disorders of the endocrines cannot affect the fetus because of compensation by the mother. It might be assumed that since the condition is definitely familial, derangements of the maternal glands might be a factor, but in most cases not all the offspring in a family are involved. In cases where roentgenograms have been taken of the skull, the sella has not been found unusual. The co-existence of so many varied signs is against the possibility of a pituitary fault.[10]

The only other endocrine gland upon which the blame might be placed is the parathyroid. It might be thought possible that the skeletal anomalies of the condition are due to a disturbance of calcium metabolism. However, no evidence of such a pathogenesis was found in any of the cases in the literature.

Several authors have likened arachnodactyly to mongolism, apparently because a few cases were reported with narrow palpebral fissures. This idea is not acceptable, especially in view of the truth that the great majority of cases are of normal mentality.

The condition is similar in some respects to congenital muscular dystrophy and it is true that the two must be closely allied. In true congenital muscular dystrophy, however, there are rarely other congenital anomalies. Young reported that in arachnodactyly the muscular electrical response was fairly normal, as opposed to the poor response in muscular dystrophy. The typical case of primary muscular dystrophy begins in youth and is progressive; progress of the dystrophy in arachnodactyly has never been reported.

The most popular conception of the pathogenesis is that there is a selective dystrophy of the mesodermal tissue. On this basis Weve explained the involvement of the bones, tendons, ligaments, muscles, connective tissues, fat, heart, and blood vessels. Other authors have recognized this explanation but felt that the idea of mesodermal dystrophy did not satisfactorily explain the involvement of other tissues which are not mesodermal in origin. Kallius [11] felt that mesoderm, ectoderm, and entoderm were all involved. As we will point out later, it is possible to explain all the findings on the basis of mesodermal maldevelopment.

Piper and Irvine-Jones [12] expressed a more general conception of the etiology. They felt that a disease entity with so many and varied manifestations must be due to pathologic defects of the germ plasm originating in embryonic life when dependence on the maternal organism is complete. The hereditary nature of the disease is clinically undisputed and Weve feels that whatever the direct cause may be there is a hereditary factor.

As to the symptoms we find the extremities long and slender. The involvement increases distally and the phalanges and metatarsals and metacarpals are unusually long and thin and tapering.

Roentgenograms show the unusual thinness and slenderness of the long bones of the hands and feet, but otherwise are usually negative. In most reports the bony structure has been recorded as normal, although a few observers have noted an increased rarefaction and decalcification. The length of the long bones of the arms and legs is not only increased as compared to that in normal persons but there is also a relative increase in proportion to the length of the trunk. Webbing of the fingers is often present and acrocyanosis of the extremities has been reported frequently. The muscular development of the whole body seems to be deficient, the general muscular weakness sometimes being so great that it has been compared with that of amyotonia congenita and congenital muscular dystrophy. Most authors find kyphoscoliosis which increases as the patients grow and is due to the great muscular weakness rather than to any changes in the bony spine. Laxity of the joint ligaments is frequent; most patients exhibit hyper-extensibility of the joints, and dislocations are not unusual. Flexion contractures are due to contractions of the tendons and occur most often in the fingers. The thorax is usually of the asthenic type, flat, narrow and funnel-shaped, with delicate ribs. The scapulae are winged. The skull in most cases is dolichocephalic, although Piper and Irvine-Jones reported a case in which the skull was brachycephalic. The ears may show abnormalities in size or shape of the lobes. Usually the bony palate is highly arched. The calcaneus is occasionally spurred.

The occurrence of congenital anomalies of the heart and lungs seems not to be unusual. Two cases have come to necropsy. Boerger's case [13] showed a patent foramen ovale, and only two lobes in the right lung. In Piper and Irvine-Jones' case congenital lesions of the heart and failure of normal divisions of the lungs into lobes was found. Besides these cases, others [10,13, 14, 15, 16] showed clinical evidence of heart disease. Also in this regard it is interesting to note that several reported cases have died of pneumonia.

The ocular signs in arachnodactyly are most interesting and form a definite part of the clinical picture. The most frequent finding is the congenital dislocation of the crystalline lens. Weve found this defect in 25 cases in 1931. In our review of 105 cases in the literature it has appeared 45 times although possibly some of the cases are repetitions. Weve felt after thorough study that Pfaundler's case [14] was identical with Boerger's first

case,[13] and that Cameron's case [17] had previously been reported by Ormond and Williams.[18] It is also possible that Fleischer's [19] and Thaden's [20] cases were identical. In our review we ignored these possibilities and considered all reported cases as distinct. The dislocation is usually bilateral and is always congenital though it may not be noticed for years after birth. The lens may be found luxated in any direction. Two cases (Thaden and Weve) have been noted where the luxation was completely into the vitreous and one of our own cases was found in this serious state. Others have reported a dislocation into the anterior chamber and this complication occurred in one of our own cases also. The incidence of ectopia lentis in arachnodactyly is probably considerably higher than 50 per cent. In the earlier cases the defect was not looked for and in other cases the eyes were not mentioned. In only 14 cases were the eyes reported as being normal and in some of these the recorder mentioned that the pupil did not respond well to mydriatics and a good intra-ocular examination was therefore impossible. A few authors [2, 19, 20, 21] have noted that the lens is almost always reduced in size. King noticed a coloboma of the lens in two cases and Weve also mentioned the occurrence of this defect.

The pupil is often small and sometimes ectopic. The iris shows a sluggish response to the instillation of mydriatics. Doubtless this is due to maldevelopment of the dilator pupillae muscle. Iridodonesis is present in cases showing ectopia of the lens. Paralysis of accommodation has been reported by Weve and pupillary membrane remnants are found fairly frequently.

Other ocular signs in arachnodactyly are not consistently present. Although in some cases the refractive findings were not recorded it seems that most of the patients were myopic, sometimes the myopia being as high as 60 diopters (Weve). Boerger's first case showed a myopia of 16 and 20 diopters in the right and left eye respectively. Cameron, Ormond and Williams, Thaden, and de Hass [22] reported cases with high myopia. In contrast to this, Bier's case [23] (in which there was no luxation of the lenses) showed a hyperopia of 9 diopters in each eye and Padovani's case [24] and several of Weve's were hyperopic. The refractive error cannot be given too great consideration in any case, however, since it may often be influenced by the abnormal position of the lens. Piper and Irvine-Jones recorded the occurrence of short lower lids in their patients. Nystagmus has been frequently mentioned and is probably due to the poor vision which most of these patients have. Other ocular signs such as nystagmus, fundus lesions, and megalophthalmos which have been mentioned, probably do not occur with greater frequency than in other groups of patients. Usually the orbits are large and there is a small amount of orbit fat, producing a sunken appearance of the eyes, which together with the long, thin face gives the patient an aged look and an appearance of suffering.

If any ocular manifestations throw light upon the etiology it must be

the ectopia lentis, since this occurs more often than other ocular defects. As noted above, the most generally accepted theory of the arachnodactyly is that the disease is due to a selective mesodermal dystrophy. The theory has been rejected by some investigators, however, since there are tissues involved (lens, zonular fibers, and iris) which are not mesodermal in origin. It can, however, be shown that the ocular defects in arachnodactyly may be explained on the basis of a mesodermal maldevelopment. There are two ways in which this may be done.

It is supposed by Treacher Collins [25] that the fibers of the suspensory ligament of the lens are originally cellular adhesions between the lens and ciliary processes, and that as the eye grows these stretch and develop into fibers. Dislocation of the lens could then be due to defective development of the suspensory ligaments in the third or fourth month of fetal life. If the adhesions are weak or absent in one part of the circumference of the lens, then the fibers opposite, instead of stretching will pull the lens in that direction. If the suspensory fibers are absent they will not be seen in the pupillary space attaching to the free border of the lens. According to Ida Mann [26] " the main factor in the production of absence or weakness of the suspensory ligaments appears to be a persistence for an abnormally long time of one, several or all of the vessels which usually connect the *circulus arteriosus iridis major* with terminal branches of the hyaloid artery around the edge of the optic cup. These vessels appear at the fifth week and begin to disappear at the middle of the third month of embryonic life. It appears then that such a defect as coloboma, or weakness of, the zonular fibers is due to causes arising in the second or third month—are remote from endocrine causation—and are developmental anomalies." It is seen from this that congenital dislocation of the lens can be explained by an anomaly of the embryonic vascular system, a mesodermal derivative. There are cases of arachnodactyly reported which showed ectopia lentis, in which the zonular fibers could be seen in the pupillary space attaching to the border of the lens. In these cases the ectopia lentis was obviously not due to absence of the zonular fibers but it could have been due to weakness of them. Moehlig is in agreement with this idea. He says, " the lens, while it is ectodermal in origin, could readily be affected by the mesodermal supportive tissues being weakened." [32]

Perhaps a better way to explain the ocular defects was mentioned by Weve. He expressed the opinion that the dislocation of the lens is not due to a defect of the zonular fibers but rather to the small size and spherical shape of the lens. Since in many reported cases the zonular fibers were normal, this idea is acceptable. Passow pointed out that this microphakia could be a manifestation of a general mesodermal dystrophy. We know that the embryonic lens is surrounded by a rich vascular membrane, the *tunica vascularis lentis,* the anterior part of which is the pupillary membrane. The arteries of this tunic, as well as those of the iris, originate from the

long posterior ciliary arteries and anastomose with branches of the hyaloid artery. Hence it is conceivable that any dystrophy of the mesoderm in embryonic life could cause dystrophic changes in the *tunica vascularis lentis* (a mesodermal derivative) and so to the lens and the iris.

We have suggested here a theory of the causation of arachnodactyly which explains all the usual findings in the disease. The theory is not new: we have only endeavored to adapt it to the whole picture. A brief summary of the salient features of the literature on the subject and reports of five cases are also presented.

Part II. Status Dysraphicus and Its Relation to Arachnodactyly

New significance has recently been attached to arachnodactyly by Passow.[27] He considers arachnodactyly as identical or closely related to status dysraphicus, or "microform of syringomyelia," basing his belief on the similarity of the signs and symptoms of the two conditions. The entity of status dysraphicus being practically unknown in the American literature it seems necessary to give here a brief outline of the condition before discussing Passow's idea of its similarity to arachnodactyly.

The first suggestion that faulty closure of the neural tube (spinal dysraphy) might be an etiological factor in many of the hereditary neurological diseases was made by Henneberg, who demonstrated that in syringomyelia the spongioblastomas are united at the spinal raphe. He felt also that syringomyelia was a dystrophy of the spinal cord.

Syringomyelia consists in the proliferation of glial cells in the central region about the central canal of the spinal cord and medulla. This central gliosis characteristically breaks down into a cystic cavity. It is believed (Henneberg) that the gliosis arises from embryonic cell rests in the spinal cord, such cell rests being present because of faulty closure of the neural tube. Hence the term "dysraphy."

Following the recognition that syringomyelia is a dysraphy of the spinal cord Bremer [28] searched in patients with syringomyelia and in their families for developmental anomalies which would seem to result from a spinal dysraphy. He found a considerable number. There was a preponderance of the span of the extended arms over the body length. One of the most characteristic signs was the funnel chest and almost invariably associated with this defect he found acrocyanosis. The hands were usually moist and cold. Further there was frequently a kyphoscoliosis which might be due either to trophic or muscular disturbances. Winged scapulae and webbed fingers were of more than occasional occurrence. Another frequent and quite typical sign was a difference in the mammae, one mamma being smaller than the other and the mammilla showing less pigmentation. Finally there was spina bifida often associated with enuresis nocturna, anomalies of the ears, highly arched palate, and other signs usually referred to as stigmata of degeneration.

Bremer found these signs not only in cases of typical syringomyelia, but also in quite a number of " normal " people, and, whenever he found one of these symptoms there was always an accumulation of others belonging to the same group. None of these cases could be diagnosed as true syringomyelia though most of them showed some disturbances of pain and temperature sensation, and quite frequently some anomalies in the muscular system. But the characteristic symptom of syringomyelia, the progression, was absent in all of them. On examining other members of the family, typical syringomyelia was found in several instances, and almost every member of the family showed some of the symptoms described above. All these facts led Bremer to assume that there is a well defined syndrome that is definitely hereditary in character and that forms a continuous line from the normal individual to the definitely pronounced case of syringomyelia.

Since most of the structures involved, the sternum, the breasts, the spine and spinal muscles, the palate, and the spinal cord are midline structures he calls this syndrome " status dysraphicus " believing them to be due to faulty formation of the spinal raphe.

It was of course difficult to draw any conclusions as to the pathological changes that took place in the spinal cord of these patients, since they were of no serious nature and did not come frequently to autopsy. Therefore Bremer [29] followed all the cases which came to autopsy in the Pathological Institute in the University of Munich for some time and picked out those which showed any suggestive sign of status dysraphicus. He examined four cases, three of which showed increased glial tissue in an area which lay behind the central canal but did not reach the posterior horns. The difference between these and normal sections of the cord was not absolutely significant, only a few glial cells and mostly fibers being seen. The fourth case showed hydromyelia of the spinal cord. The changes were mostly in the cervical portion, few alterations being observable in the lumbar region. The most significant feature was a proliferation of the ependyma in the central canal. Examining relatives of these cases, in each particular family a few members could be found who revealed the typical picture of status dysraphicus.

The clinical picture of status dysraphicus was first brought to the attention of the ophthalmologist when Passow [27] published his classical studies in 1933. In addition to mentioning the general symptoms of status dysraphicus described by Bremer, he noted also the frequent occurrence of Horner's syndrome and heterochromia iridis. In 50 patients with Horner's syndrome and heterochromia he found signs of status dysraphicus in 80 per cent. Later he added more cases and in the whole series found signs of status dysraphicus in an even higher percentage. Anomalies of the sternum, especially funnel thorax, were common. Kyphoscoliosis, winged scapulae, and webbed fingers occurred frequently, often together. In most patients the span of the extended arms was greater than the body length. Differences in the size and position of the breasts were noted.

In fairness to the facts it should be mentioned that Horner's syndrome and heterochromia, while being found not infrequently in status dysraphicus do not occur as often as it may seem from reading this review. In most textbooks Horner's syndrome and heterochromia are given hardly more than passing mention as symptoms in syringomyelia. Bremer in his studies found them in only a low percentage of cases of status dysraphicus. In this review we have stressed their occurrence since they are of great interest to the ophthalmologist. Passow's work gives the impression that these symptoms occur with greater frequency than is really the case. In searching for cases of status dysraphicus Passow used these symptoms as a guide and accordingly they occurred in a high percentage of his cases. It does not follow that they occur in all or most cases of status dysraphicus.

Passow felt that these cases offered clinical proof that the Horner's syndrome and the heterochromia could be explained by the same etiology as the other symptoms of status dysraphicus. He attempted also to supply experimental proof. Up to that time the question of whether heterochromia iridis might be the result of sympathetic paralysis had not been definitely settled. Many authors were unable to produce a depigmentation of the iris by sympathectomizing animals. Other investigators on the other hand had shown that interruption of the cervical sympathetic resulted in heterochromia. Passow, in his thorough experiments, showed that heterochromia followed a paralysis of the cervical sympathetic only when the paralysis occurred before development of the anterior layer of the iris and its pigment. He excised a portion of the right cervical sympathetic in young animals. Two or three months after the sympathectomy a lack of color was perceptible in the homo-lateral iris in those animals which were between six and eight days old at the time of the operation. In older animals, however, no heterochromia developed. Microscopical study of those irides which showed heterochromia revealed a decrease in (1) intensity of the anterior pigmented border layer, (2) number of chromatophores in the stroma, (3) intensity of the pigment layer. These changes were without evidence of inflammatory process. Passow concluded then that as Horner's syndrome is dependent on a disturbance of the motor fibers of the cervical sympathetic, so heterochromia is dependent on a disturbance of the trophic-vasomotor fibers.

Of course cases of acquired heterochromia and Horner's syndrome cannot be included in this group. While Passow has shown that Horner's syndrome and heterochromia frequently occur in status dysraphicus and are a result of sympathetic paralysis due to the dysraphy, there are nevertheless cases of Horner's syndrome and heterochromia which have no relation to status dysraphicus. Paling of the iris may follow trauma, or severe inflammation, or it may be a result of the ordinary workings of senility. Likewise Horner's syndrome is not found exclusively in status dysraphicus or syringomyelia, but may occur in association with various other diseases of the cervical cord and medulla, and in various lesions of the neck. A

quite satisfactory summary of these factors is given in a recent article by DeJong.[30]

The facts so far mentioned reveal that status dysraphicus is a distinct clinical entity. It is of interest to the ophthalmologist because of the frequent occurrence of Horner's syndrome and heterochromia iridis.

The similarity of the signs and symptoms of arachnodactyly and status dysraphicus becomes apparent as soon as one becomes familiar with the two conditions. Passow [27] pointed out this similarity in 1935. In arachnodactyly there is an over-length of the extremities, particularly of the hands and feet. The fingers and toes are unusually long, thin and tapering. In status dysraphicus the arms are too long and the span of the extended arms is greater than the body length. The hands are usually hypertrophic but in some cases may be very gracile. Web formation of the digits, funnel thorax, anomalies of the spine, winged scapulae, highly arched palate and anomalies of the external ears are common to both syndromes.

The eye findings, however, seem to be entirely different in the two conditions. In arachnodactyly we find congenital luxation or subluxation of the crystalline lens and poor reaction of the iris to mydriatics. In status dysraphicus there are heterochromia of the iris, Horner's syndrome and occasionally cataract formation. While the analogy of most of the symptoms suggests the relation of the two complexes, the ocular findings seem to show the contrary. It is possible, however, according to Passow to bring the eye findings of the two conditions together on the same basis. As was shown in the first half of this paper it is possible to explain all the findings in arachnodactyly, including the ocular, on the basis of a mesodermal maldevelopment. In status dysraphicus, the eye findings are explained by Passow as being the result of a dysraphy of the spinal cord, producing a paralysis of both motor and trophic-vasomotor fibers of the cervical sympathetic. And he believes all the symptoms of the disease are to be explained on a similar basis. As already mentioned, Weve [2] always found the lens in arachnodactyly very small, and the dilator pupillae muscle undeveloped. Passow explains these defects, as well as the ocular defects of status dysraphicus on the same basis. In embryonic life the lens is surrounded by a vascular membrane, the blood supply of which arises from the long posterior ciliary arteries. A dysraphy then, says Passow, could cause Horner's syndrome through paralysis of the motor fibers of the cervical sympathetic, heterochromia through paralysis of the trophic-vasomotor fibers of the sympathetic, and microphakia and ectopia lentis through trophic vasomotor disturbance of the tunica vascularis lentis in embryonic life. Actually an atrophy of the pigment layer of the iris and persistent pupillary membrane are quite frequent findings in arachnodactyly, as already mentioned by Weve [2] and Igersheimer.[21] Passow showed that after experimentally produced sympathetic paralysis in young animals there occurred not only Horner's syndrome but also a dystrophy of the entire iris, the ciliary body and the zonules.

It follows that one should be able to demonstrate cases of arachnodactyly showing evidence of status dysraphicus and vice versa. In reviewing the literature we found a few such cases mentioned, but, since status dysraphicus has been known for only a relatively short time, most observers simply did not look for signs of this anomaly in their cases of arachnodactyly. Brock [31] in his case of arachnodactyly observed acrocyanosis, funnel thorax and spina bifida. Carrau,[7] Weber,[33] and Boerger [13] reported cases of arachnodactyly showing funnel thorax and kyphoscoliosis. Muscular weakness was often reported and this in some cases might be construed as a symptom of status dysraphicus, especially if the muscles involved were of the spinal group. We were unable to find any case of arachnodactyly with heterochromia iridis. One case was reported, however (Boerger), which may have had a Horner's syndrome. In this case he reported that the right lid fissure was somewhat larger than the left and the right bulb more prominent. We can only hazard an opinion that what this case actually showed was a small palpebral fissure and enophthalmos of the left eye (Horner's syndrome).

Passow reports two cases of his own which strengthen his idea of the similarity of the two conditions. The first, a 14-year-old girl, had spider fingers, luxation of the lens and eccentric pupils as well as heterochromia iridis and a difference in the size of the mammae, the smaller mamma being on the side of the paler iris. The hands were moist, cold and livid, there was deformity of the spine, webbing of the fingers, highly arched palate and increased reflexes. The second case, a 20-year-old boy, had spider fingers, luxation of the lenses and a heart lesion as well as overlength of the arms and heterochromia iridis. As to other symptoms he had funnel thorax, winged scapulae, and webbed fingers.

Summary

Arachnodactyly is a little known developmental disease due probably to a maldevelopment of the mesodermal derivatives. Status dysraphicus is a distinct clinical entity to be explained on the basis of a mild form of syringomyelia. There are so many characteristics typical to both arachnodactyly and status dysraphicus that there is a reasonable excuse for believing the two diseases to be identical or at least closely related from an etiological standpoint. Passow's idea of the similarity of the two diseases has so many points in its favor that further reports are desirable either to confirm or disprove the theory.

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CLINICAL MANIFESTATIONS AND STUDIES IN PARENCHYMATOUS HEPATITIS *

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It is a paradoxical fact that one of the most accessible and important organs of the body, the liver, is the one about which the least is known. The multiplicity of its functions is appreciated but little understood. Therefore, for practical as well as theoretic purposes, any data concerning liver function, metabolism and pathology are deserving of record.

The baffling part of the liver problem lies in our inability to reproduce in animals conditions frequently found in man. Liver necrosis, hepatitis, cirrhosis, atrophy and regeneration have all been reproduced experimentally with varying degrees of success. These experimental lesions and their effects have been carefully studied. Yet none have been observed that satisfied every criterion. When morphologic alterations are produced, the physiologic changes may not strictly parallel those observed in man, in corresponding diseases; and vice versa.

Results approximating those seen in man have permitted simultaneous studies upon the pathologic histology and the physiologic chemistry. These studies have been carried on in animals suffering from acute or from prolonged liver damage induced by various types of hepatotoxins. In making comparisons, care must be taken in drawing conclusions, because powerful liver poisons produce disproportionate changes in different species. Furthermore, it has been shown that the previous diet of the experimental animal may, to a large degree, influence the results.

Among the many known chemical agents used to produce parenchymal liver damage, the effects of the hydrazine group have been extensively investigated. Bodansky, Underhill, Lewis and Izume have studied the action of the hydrazines upon liver metabolism in animals. They have shown that chronic intoxication with hydrazine and certain derivatives has interfered with the glycogenic function. Wells was able to show that hydrazine and its derivatives produced parenchymal injury to the liver of animals. The architectural structure of the liver was changed by early damage of the cells in the center of the lobule. The injury then extended to the periphery of the lobule, ultimately resulting in diffuse fatty changes. Wells in his early work stated that whereas other substances, such as the heavy metals, produced changes in other parenchymatous organs of the body, hydrazine limited its effects solely to the liver. Subsequent experiments have shown that this rather unique effect of hydrazine may be produced by a few other substances. In our series of animals studied thus far, acute intoxication pro-

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duced hepatic injury only. In man, however, chronic hydrazine poisoning resulted in changes in other tissues.

In addition to the histological changes in the liver parenchyma, hydrazine exercises another very important effect, namely that upon the glycogenic function of the body. Underhill and his co-workers as early as 1908 began studies of this problem. They noticed the marked hypoglycemia that results from the administration of hydrazine sulphate. This reduction in blood sugar was accompanied by an almost total disappearance of glycogen from the liver and from the muscles of the body. Underhill could offer no explanation for this effect. Bodansky, using the levulose tolerance test as a measure of hepatic injury, carried on extensive investigations of the variations in degree of liver damage produced by hydrazine and by certain hydrazine derivatives. His observations, which agreed with those of Wells, indicated that hydrazine sulphate produces fatty degeneration of the liver with almost complete disintegration of the hepatic cell without much apparent damage to other organs of the body. However, more complicated hydrazine derivatives and notably phenylhydrazine, when given to the experimental animal in quantities sufficient to cause "liver death," produced early changes in other organs of the body, notably in the kidneys, the spleen, and the bone marrow. He concluded that the hydrazine group constituted a powerful protoplasmic poison that acted chiefly upon the liver and seriously interfered with its glycogenic function.

Later, Izume and Lewis investigated the entire subject again. They concluded that hydrazine not only prevents the transformation of non-carbohydrate material into glucose and glycogen, but also prevents the synthesis of glycogen from glucose. This interference with glyconeogenesis interrupts the process of storage of glycogen in the liver. As a result the muscles are starved owing to the inability of the body to mobilize glycogen for their use. This condition is identical with that which Mann and his coworkers described in the completely hepatectomized animal. Intoxication with hydrazine and its derivatives results in a failure on the part of the body to form glycogen from glucose, from protein derivatives, and from fatty acids. That the synthesis of lactic acid is prevented also seems probable.

It was my good fortune to have the opportunity of studying the effects of a chemical compound from which hydrazine may be derived on two men exposed to the vapor of a nitrosamine. These two patients had repeatedly inhaled this chemical poison in sufficient amounts to produce headache, backache, abdominal cramps, nausea, anorexia, weakness, drowsiness and giddiness. They were poisoned in a rather unusual manner. Both were engaged as chemists in the production of dimethylnitrosamine to be used as an inhibitor for the prevention of corrosion. Their contact with this chemical substance was chiefly by inhalation. The first patient was assigned to the task of development and manufacture of dimethylnitrosamine. While engaged in this he became ill and could not continue his work. He

left the employ of the company for the purpose of seeking medical aid. It was approximately 16 months later that the second man was assigned to resume the production of the substance, at the point where the first chemist stopped. It was not until the second man developed symptoms and signs identical with those observed in the previous case, that the cause of these symptoms was suspected. The second man's intoxication followed repeated inhalations and the wiping up of a quantity of the substance that was accidentally spilled on the floor. He was the more severely affected of the two and died following an exploratory operation. Others who had worked in the same laboratory and had more or less contact with the suspected chemical substance were interviewed. All of them gave some history of dizziness, faintness, headache and weakness.

Case Reports

Case 1. T. C., chemist, aged 29, single. The chief complaints are pain in the upper right quadrant, nausea, a sensation of weakness in the upper abdomen, and occasional abdominal cramps. He had cerebro-spinal meningitis at one year, and pneumonia and pleurisy at seven years. In 1925 he sustained an injury to one of his cervical vertebrae. In 1932 he suffered from what was diagnosed as "colitis" and anal fissure. He dates the beginning of his present illness to about July 1933, at which time he was engaged in the making of dimethylnitrosamine for commercial use. It was during the development of this synthetic compound that he began to feel ill. The patient states that on August 2, 1933, after he had been exposed daily to the fumes of this substance, he began to believe that the inhalation of it was making him ill, and he reported the fact to the company physician on that day. However, he continued to work irregularly up to August 15, when he felt so ill that he decided to quit. He complained of exhaustion, headache, cramps in his abdomen, deep soreness in his left side, nausea, some vomiting, occasional backache and utter fatigue. August 16 he noticed that his abdomen was distended and reported it to his physician who sent him into the hospital for further observation. On August 20 a paracentesis was performed and about two and a half quarts of fluid were withdrawn. Although the abdomen slowly filled again, no further tapping was resorted to. The patient states that he was told that he had "peritonitis," and that it probably was tuberculous in origin. He entered a sanatorium in Newburg, N. Y. Although he remained distended for some time no further paracentesis was performed. He remained in the tuberculosis sanatorium until January 1934, at which time he was discharged. Careful examination revealed no evidence of tuberculosis and the patient was returned to his home where he sought further medical advice because of the persistence of headaches, abdominal pain, and weakness. He remained in bed at his home until April 16, 1934, and then left to consult physicians in a large clinic in a hospital in New York City. He was thoroughly examined but nothing was found. A submucous resection was advised and was performed on May 25, 1934. He returned home to a small town in New York State, with instructions to rest. He rested all summer, enjoying a maximum of sunshine. Gradually the attacks of pain became less frequent. The patient states that he was jaundiced at the beginning of his illness. He also thinks that he had a short period of jaundice in the early part of January 1935. He is sure that he never had any fever. He has slowly regained his weight, which at one time he believes was about twenty pounds under his average. He admits that the entire illness has made him somewhat nervous and depressed. There is no history of clay colored stools. He does not remember passing dark urine.

His habits are good. He rarely takes alcohol. Smoked very little prior to 1933 and not at all since. He is a moderate eater. There is no history of tuberculosis, cirrhosis, or of any degenerative diseases in his family. His parents and brothers are all living and well.

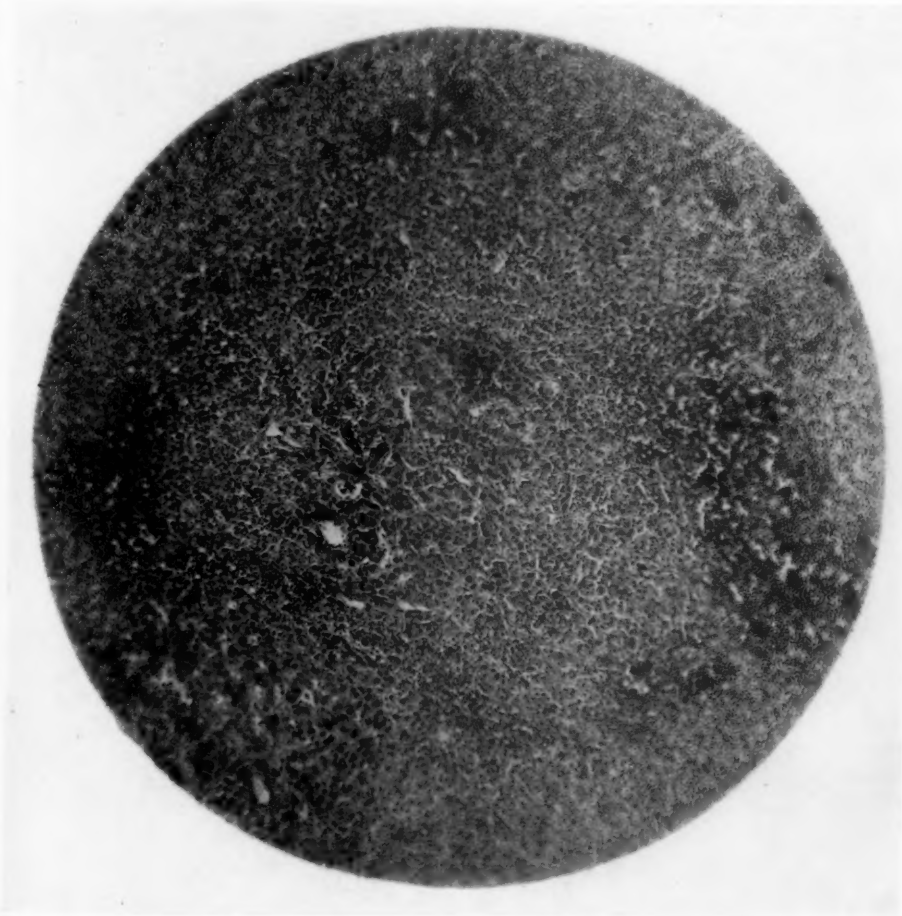


FIG. 1. Diffuse liver injury with multiple miliary hemorrhages.

Physical examination reveals nothing of importance about his head, neck or chest. Blood pressure 132 systolic and 68 diastolic. His abdomen is slightly above the level of his ribs, and shows a moderate panniculus. There is tenderness throughout the whole abdomen on light palpation, especially in the right upper quadrant where there is definite muscle spasm. The liver is felt two fingers-breadth below the margin of the ribs; it is moderately firm and tender. The spleen is not felt. All reflexes and tests of sensation are normal. The non-protein nitrogen is 40 mg. per cent. Blood sugar taken in the middle of the afternoon, after his noon day meal, was 66 mg. per cent. Kahn test negative.

The patient promised to return for more study, but was not seen again until February 17, 1936, when he entered Harper Hospital. Physical examination at this time did not differ from the one made eleven months before. Studies of his blood and blood chemistry on this occasion were as follows:

Blood Count: Hgb. (Newcomer) 84 per cent. Erythrocytes 3,680,000. Leukocytes 7,000. Color Index 1.1. Reticulocytes 1 per cent. Thrombocytes 349,400. Differential Count: Metamyelocytes 3 per cent; neutrophiles, stab. 20 per cent; neutrophiles, segm. 26 per cent; eosinophiles 0; basophiles 1 per cent; total of granulocytes 50 per cent; lymphocytes 48 per cent; monocytes 2 per cent.

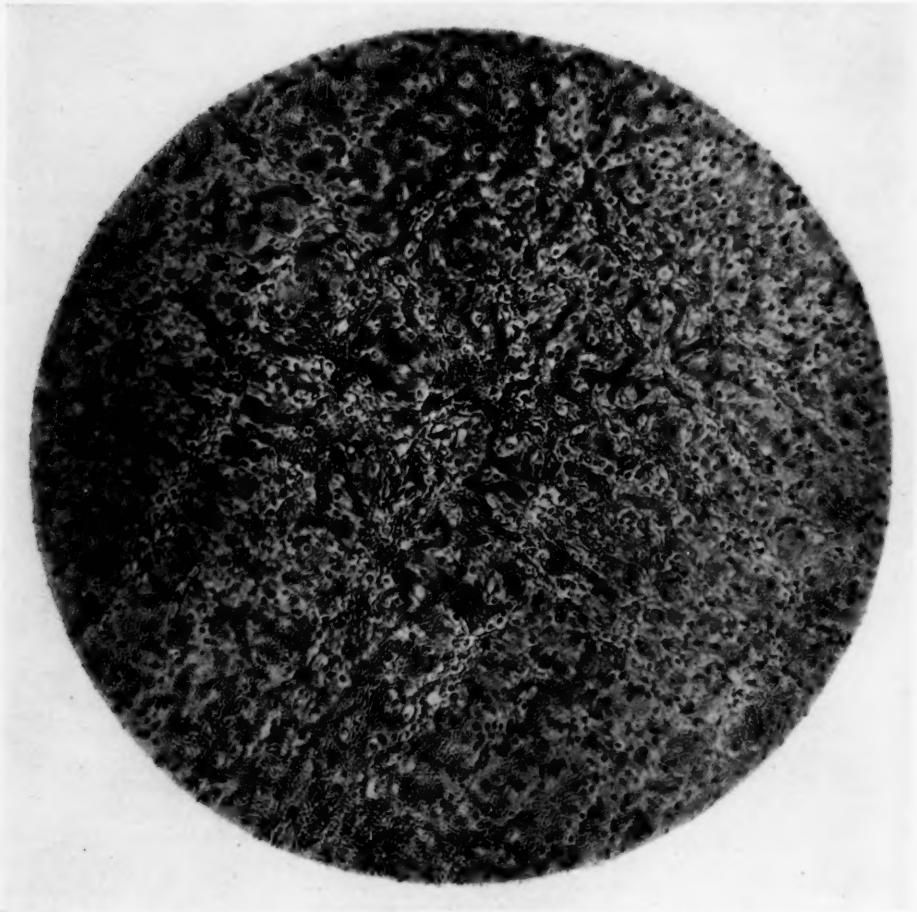


FIG. 2. Acute intoxication with liver cell destruction. Hyperchromatic and pyknotic nuclear changes.

Urinalysis: Fresh specimen; color yellow; reaction acid; sp. gr. 1.015; albumin 0; sugar 0; urobilin 0; acetone 0; diacetic 0; bile 0. Phenolsulphonephthalein test: Normal output and curve. Non-protein nitrogen 30.9 mg. per cent; icteric index 8; calcium 10 mg. per cent; phosphorus 2 mg. per cent. Van den Bergh: Direct, negative; indirect, slightly positive. Takata-Ara test; negative. Albumin-globulin ratio 9.43/4.95. Numerous blood sugar tolerance curves were done, all of which showed an increased tolerance. Bromsulphalein test showed normal maximal dye elimination. Kahn test negative. Basal metabolic rate plus one. Gastrointestinal roentgenograms revealed no abnormal findings. Cholecystography revealed a normally functioning gall-bladder.

During the patient's hospitalization, the pulse rate averaged 80. There was no elevation of temperature.

Case 2. H. B., aged 26, white, single, chemist, complains of pain in his abdomen, weakness, lack of appetite and headache. He dates the beginning of his illness from December 1, 1934, at which time he began working on the job of pro-

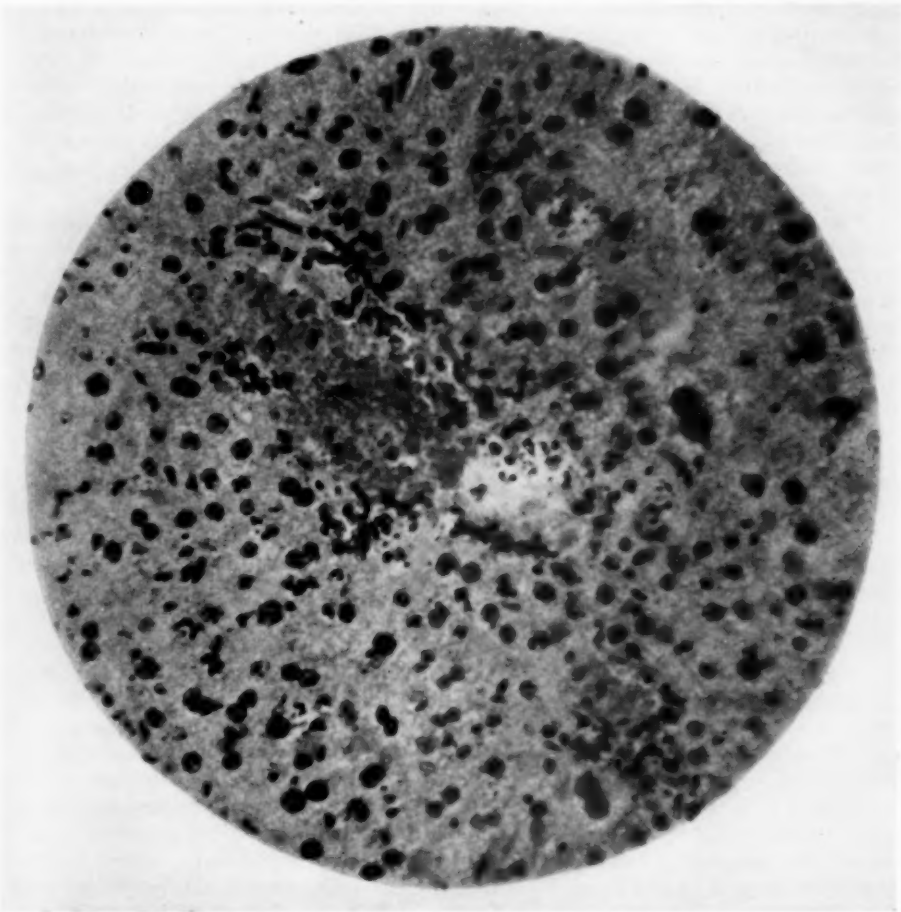


FIG. 3. Diffuse parenchymal injury showing nuclear changes in liver cells; mitoses; beginning leukocytic infiltration and thromboses in the small veins.

ducing nitrosamine. On December 12, 1934, he dropped a flask containing about one liter of this substance, spilling the contents. He used an ordinary mop and rag to clean up the fluid. He was very ill that night and the next day unable to return to work. About December 18 he began to have pain in his upper abdomen, cramps and a feeling of distention. He became constipated. About December 20 his abdomen became more tender and the distention grew progressively worse. There was a marked loss of appetite, slight nausea, but no vomiting. He is uncertain as to the time that his skin became yellow, but believes that it began simultaneously with the enlargement of his abdomen. His past history is unimportant. There is no previous record of respiratory, cardiac, renal or gastrointestinal diseases. He smokes 20

cigarettes per day, rarely uses alcohol. There is no history of cirrhosis, cardiac, renal or vascular disease in his family. He entered the hospital on December 26, 1934.

Physical examination revealed an acutely ill patient, lying quietly in bed, pale and somewhat emaciated. The sclerae were slightly icteric; examination of the head was otherwise negative. Examination of the lungs revealed signs of free fluid in each pleural cavity. The heart was not enlarged; the heart sounds were clear and of good quality. Blood pressure 120 systolic and 76 diastolic. Nothing noteworthy was found about the peripheral vessels. The abdomen was distended and showed bulging on both sides. There was no visible venous engorgement. Both shifting dullness and a fluid wave were present. The abdomen was not rigid. The margin of the liver could be felt on palpation about three fingers below the right costal edge. It was tender. No other organs or masses were palpable. The genitalia were normal; no masses felt in the testes. Prostate and seminal vesicles normal.

On December 28 abdominal paracentesis was performed and 3,500 c.c. of fluid removed. Paracentesis was performed three times afterwards, at about one day intervals; 6,000 c.c. was the largest amount removed. Two c.c. of salyrgan were given intravenously daily for five days beginning January 10. At no time did the temperature rise above 99.2°. The pulse varied between 80 and 100, and the respirations between 20 and 26. I saw the patient in consultation on January 20. My examination confirmed the previous findings in all respects. On the following day paracentesis was again performed and 5,000 c.c. of fluid obtained.

Laboratory Findings: Urinalysis (Jan. 4, 1935): Fresh specimen; amber; clear; acid; sp. gr. 1.022; albumin trace; sugar negative; acetone negative; occasional hyaline cast; occasional pus cell; no red blood cells. Blood count (Jan. 24): Hgb. 80 per cent; erythrocytes 4,600,000; leukocytes 9,900; polynuclears 72 per cent; small lymphocytes 28 per cent; some variation in the shape and size of the red blood cells. Blood chemistry (December 28, 1934): Icteric index 16; van den Bergh reaction, faintly positive, direct and indirect. Kahn test negative. Roentgenogram of chest (Dec. 27, 1934): Slight elevation of the right diaphragm. There is apparently a pneumonitis in the right base. Fluoroscopic examination shows movement of the right diaphragm. The remainder of both lung fields is clear. There is no evidence of pulmonary tuberculosis. Examination of ascitic fluid: Sp. gr. 1.010; Wright's stain of centrifugated fluid showed a few red blood cells, and 61 per cent polynuclears and 39 per cent lymphocytes. Kahn test negative. Non-protein nitrogen 22.2 mg. per cent. Albumin 0.35 grams; globulin 0.38 grams; fibrinogen negative. Total protein 0.73 grams. Calcium 9.78 mg; phosphorus 3.55 mg.; cholesterol, faint trace present. An exploratory laparotomy was performed. Summary of data recorded by surgeon: "Large amount of yellowish ascitic fluid. Liver extremely engorged, about a hand's breadth below margin of rib, smooth and purplish in color. Spleen markedly engorged and lobulated, purplish in color. Gall-bladder and duct somewhat thickened; no stones; emptied readily. Omentum retracted with many adhesions to the abdominal viscera. Appendix buried in a mass of adhesions. The pancreas appeared normal. The peritoneum and the mesentery were smooth and not injected. No tubercles were seen. The patient stood the operation poorly." He died on January 28.

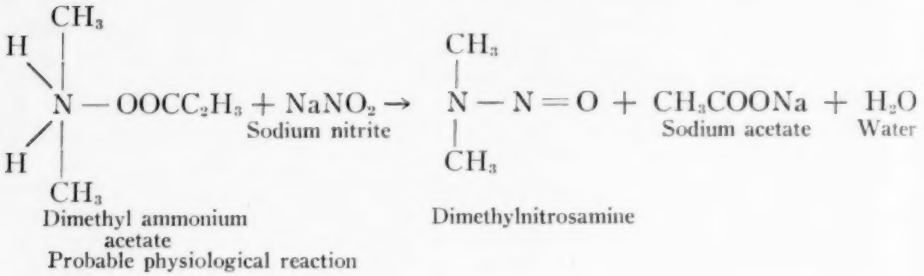
Autopsy: I am indebted to Dr. Lewis for the following notes. (Only data bearing on the condition are recorded.) Postmortem suggillation is extreme. Rigor mortis is marked throughout entire body. Conjunctivae, sclerae and the skin are slightly jaundiced. Superficial lymph glands are palpable. Right pleural cavity contains about 400 c.c. of serous fluid. Left pleural cavity contains about 100 c.c. of blood stained serous fluid. The pleural surfaces are everywhere smooth and glistening. The pericardium contains a slight excess of pericardial fluid. There are a

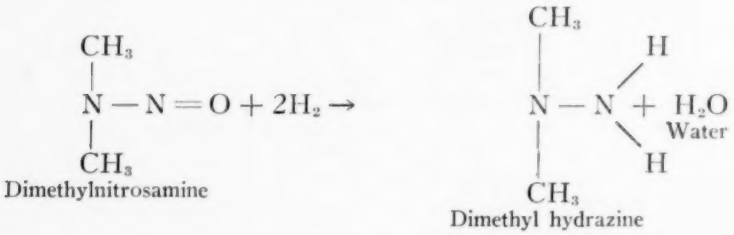
number of small subpericardial hemorrhages. The heart weighs 230 grams. The myocardium is light brown in color, very soft and flabby. There is dark blood in all the chambers; no agonal clots. Lungs: The right lung weighs 290 grams. The left lung weighs 320 grams. The left lower lobe is dark red, firm in consistency. There are small hemorrhages in the bronchi and trachea. The spleen weighs 320 grams. It is extremely soft. The pulp is uniform, mushy in consistence and rather darker than normal. There are some adhesions and some fibrinous exudate over the upper portion of the spleen. The gall-bladder contains about 20 c.c. of dark greenish-brown viscous bile. The biliary channels are patent. The liver weighs 1,380 grams. It is dark, greenish, mottled brown, rather firm in consistence. On section it presents a definite, greenish-brown, mottled appearance. The stomach is somewhat dilated. The mucous surface is thickened and the rugae are deep. In the prepyloric region there are numerous superficial hemorrhages and one small superficial ulceration, measuring 2 cm. at its greatest diameter. The duodenum, the jejunum, and the small bowel are not remarkable. The mesenteric lymph glands are markedly enlarged, and very pale and pinkish in color. The lower portion of the ileum is thickened. Its serous surface is covered by a firm, fibrinous exudate. There are occasional superficial hemorrhages scattered throughout the entire mucous surface of the small bowel. The appendix is long, retrocecal and covered by old adhesions. The adrenals are not remarkable. Kidneys: Combined weight of the kidneys is 300 grams. They are dark brown in color, the capsule is thickened and is fairly adherent to the underlying cortex. On section the renal markings are not well defined. Bladder and prostate reveal nothing abnormal. Summary of microscopic findings (P. S. Morse): Liver: Acute diffuse degeneration of the whole parenchyma with focal and diffuse areas of necrosis. The necrotic areas are infiltrated with round cells and phagocytes. Multiple periportal miliary hemorrhages. Areas of intense regenerative proliferation of liver cells with marked irregularity in size and staining reaction of protoplasm and nuclei. Kidney: Acute terminal passive congestion. Glomeruli and tubules normal. Some bile retention in tubules. Small intestines: Marked proliferative productive peritonitis. Thickening, edema and round cell infiltration of peritoneal coat. Heart muscle: Virtually normal; slight edema, no hypertrophy or muscle cell destruction, no fatty infiltration. Suprarenals: Normal cortex and medulla; no necrosis, no adenomatous zone, no small cell infiltration. Spleen: Postmortem autolysis, no cellular changes. Lymph nodes: Diffuse fibrosis, increase in size of coarse trabeculae; edema of gland as a whole, scarcity of germ centers. Bone marrow: Red marrow shows usual myeloid picture.

Animal Experiments

The nitrosamines have not been extensively used in industry. Manufacturers of the chemical had no occasion to suspect that its use, much less its inhalation, was fraught with danger. It is a clear yellow liquid soluble in alcohol, of surface tension one-sixth that of water. It has a slightly pungent, though not unpleasant odor. It is not particularly irritating to the mucous membranes. It has no corrosive action when applied to the skin.

In this instance it was intended for commercial use as an inhibitor of corrosion and a stabilizer. In the process of manufacture the following chemical steps took place:





As I was unfamiliar with the toxicity of dimethylnitrosamine and the literature contains no data bearing on the subject, it was decided to study the effects first upon mice, and later upon larger animals. A white mouse was placed in a one-liter jar, to the lid of which was fastened a gauze screen, saturated with 10 c.c. of dimethylnitrosamine. The jar was not sealed, a small amount of air being allowed to enter at the top. The immediate effect of the substance was irritation of the eyes, nose and skin, although the reaction did not seem to be a violent one. The respirations were not apparently affected. In a short time the mouse appeared sick and remained quiet. In 18 hours, mice subjected to one-half hour exposure to the fumes died in convulsions. Autopsy of such mice revealed nothing unusual on gross examination. There was perhaps slight injection of the peritoneum, some reddening of the bronchial mucosa. On microscopic examination the liver was the only tissue affected. There was diffuse regenerative hypertrophy and proliferation of liver cells. There was marked variation in shape and size and staining qualities of the nuclei of the liver cells. Marked irregularity of chromatin distribution was observed with pyknosis and autolysis.

A dog, weighing 12 kilos, was placed in a box and a small amount of air was permitted to enter. Gauze saturated with 30 c.c. of dimethylnitro-

samine was fastened to the lid of the box. The animal was kept in this chamber for 30 minutes. Except for occasional sneezing the animal did not seem to be irritated by the fumes of the substance. He was happy when removed from the box and showed no ill effects from the fumes. Eighteen hours later the dog had a mild convulsion. His blood sugar at that time was too low to read. Intravenous glucose was administered. Although the animal recovered slightly, it was impossible despite continued intravenous administration of glucose to influence the constant twitching. The blood sugar level could not be brought up to normal. The dog died in hypoglycemic shock. At autopsy gross examination revealed nothing abnormal in any of the tissues of the chest or abdominal cavity. Blood removed from the heart revealed no methemoglobin. Microscopic examination: The liver showed acute diffuse degenerative changes, evidenced by necrosis, especially in the region of the central vein with marked shrinking and acute atrophy of liver cells at the periphery of the lobule. This process had led to an enormous apparent widening of the bile capillaries. In the necrotic areas infiltration of phagocytes and phagocytosis had barely begun. Many liver cells had lost their staining quality in atrophic areas. Only the nuclei took the stain. Lungs: Acute diffuse pulmonary edema with acute terminal passive congestion. Relative atelectasis. The larger bronchi were filled with mucus and desquamated epithelium. Heart: Normal throughout.

A second dog, weighing 10.5 kilos, was then subjected to inhalations of 10 c.c. of dimethylnitrosamine for a period of five minutes daily in the same chamber. The animal did not seem irritated by the exposure. On the fourth day the dog appeared less active than he had been previously. He played about, however, fairly well. On the fifth and last day that the dog was subjected to the inhalations he seemed less active. On the sixth day the sclerae and mucous membranes were distinctly jaundiced. The urine contained a moderate amount of bile. The dog drank glucose and water freely, but refused to eat. On the seventh day the animal twitched occasionally. There was no spasticity. Vomitus of clear fluid on two occasions. The gait was somewhat unsteady but there was no paralysis.

Autopsy: There were no abnormal findings in the gross examination. Microscopic findings: The liver showed uniformly distributed diffuse hemorrhages around the central veins, which extended peripherally and did not involve the portal area. No changes were noted in the pancreas, spleen, suprarenals, kidneys and heart muscle.

Experimental cirrhosis resulting from hepatic injury has been produced in many ways. Moon has completely reviewed this subject. Of all the hydrazines only phenylhydrazine is used in the practice of medicine. Its pharmacologic action is well understood and differs greatly from that of many hydrazine salts. Hurst and Hurst were able to produce cirrhosis with ascites by the simultaneous administration of hydrazine sulphate and manganese dioxide. In their animals a diffuse parenchymal destruction took

place involving the entire liver lobule which differed histologically from the effects of dimethylnitrosamine.

In all likelihood this difference is due to the fact that dimethylnitrosamine is carried by the arterial blood to the liver cell where it exerts at least a twofold action; firstly it causes liver cell destruction and secondly it is glycogenolytic. In this respect it differs from other hepatotoxins that have been studied, and by the same token it affords another method of approach to the study of liver problems.

Summary

The chief points in our knowledge of the toxic parenchymatous hepatitis due to dimethylnitrosamine may be summarized as follows:

1. Dimethylnitrosamine is a volatile toxic substance which upon inhalation exerts a destructive action on the liver. Its use should be considered as an industrial hazard. Its immediate and remote toxicological effects have been described. It probably is reduced in the liver to a hydrazine and acts in that form.

2. The primary seat of action is about the center of the liver lobule where it produces a degenerative necrosis of the liver cell. Continued and more intensive poisoning results in the destruction of all liver cells. Ultimately partial bile duct obstruction takes place.

3. Dimethylnitrosamine destroys the glycogenic function of the liver. Hypoglycemic shock, in all respects resembling that seen in the hepatectomized dog, may be produced with dimethylnitrosamine. When recovery takes place, glyconeogenesis is impaired. Muscle glycogen reserve is diminished.

4. Two human cases are reported of toxic parenchymatous hepatitis with ascites, due to poisoning with dimethylnitrosamine. Toxic portal cirrhosis with ascites may be experimentally produced with dimethylnitrosamine.

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PAIN AND PAIN EQUIVALENTS IN HEART DISEASE *

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Approximately 90 per cent of all non-traumatic sudden deaths are cardiovascular in origin, and 65 per cent are due to coronary artery disorders. A study of these cases of sudden death demonstrates a strikingly large number who gave a history of precordial or near-by pain preceding or during the fatal illness. The majority of these show pathological evidence of antecedent changes in the coronary vessels—namely sclerosis; but these changes were not the cause of death. Some added mechanism caused a sudden cardiac standstill.

This tragic event—sudden cardiac death—is well known even to the laity, but the symptoms leading up to it are not so well known, nor is it sufficiently recognized that practically all of the earlier symptoms may be encountered in disorders not at all associated with the cardiovascular system. Of these early evidences of coronary disorder, pain is both numerically and psychically the most important manifestation. Because of this frequency of pain and its effect upon the patient's morale, a consideration of the various types of cardiac pain, their origin and distribution and associated symptoms and signs will be presented, and an attempt made to differentiate pains which are a manifestation of cardiac disorder from those arising from other tissues, and tending to cause diagnostic confusion.

At a period when anatomical changes occupied the center of the medical stage and before disturbed physiology was seriously considered as a cause of disease processes, Heberden in 1768, under the title "Some Account of a Disorder of the Breast," gave the first clear description of the condition since known as angina pectoris. He stressed the importance of nervous and mental influences and stated that this condition belongs to the class of the spasmodic, rather than that of the inflammatory complaints. Throughout the history of this disease it seems apparent that medical men are peculiarly susceptible to it. John Hunter recognized the rôle of emotional strain and wrote that his life was in the hands of any rascal who chose to annoy him. He died in a fit of temper. But that emotional strain was not the sole factor was suggested by Jenner in 1799 when he described the frequent association of angina with disease of the coronary arteries. Three years before he had seen Hunter in his second attack and suggested in a letter to Heberden this probable association.

It was not until about 50 years after Heberden's first article that Reeder (1821) suggested that many other conditions might produce a type of precordial pain sufficiently similar to justify the use of the term "pseudo-angina." From this period until the latter part of the last century there was

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little added until the writings of Mackenzie, Allbutt, Wenckebach, and Osler, who in 1897 stated that angina pectoris is "not a disease but a syndrome or symptom complex." Sir Clifford Allbutt, in a letter to Dr. Robert L. Levy [1] gave his last definition of angina pectoris: "Angina pectoris is a pain, sometimes slight, sometimes agonizing, arising usually under the sternum and referred in certain definite directions, due to stretching of the outer coat of a morbid aorta; or in a few cases of that of the heart itself. This is my first hasty suggestion for your 'definition.'"

In late years the term pseudo-angina has largely been discarded, although as recently as five years ago Harlow Brooks [2] used it to designate a condition "where anatomic defects do not exist in the heart or aorta, whereas in true angina pectoris I hold that lesions exist to a recognizable degree in practically all instances." He believed that most patients with pseudo-angina were neurotics, but appears not to have taken into account the existence of a significant number of instances of true angina pectoris in which neither physical nor electrocardiographic examination reveals unequivocal evidence of heart disease. Current writers employ the terms angina pectoris and anginal syndrome synonymously, although the present tendency is to modify the latter with a qualifying phrase as to etiology.

Throughout this later period there have been three main theories of pain production in the heart. Allbutt believed that the pain arises in aortic lesions mainly. Opposed to this was the teaching of Mackenzie that the pain was due to exhaustion of the myocardium induced by coronary artery disease. Closely related to this was the theory of Allan Burns who in 1809 attributed the pain to anemia of the heart muscle. Sigler [3] recently shows that the carotid sinus reflex is increased in the vagotonic individual and suggests that resultant coronary vasoconstriction and myocardial ischemia may be the cause of angina. At the present time, the majority of workers consider ischemia of the heart muscle as the most acceptable cause of angina pectoris. But that this is not the sole cause was shown by Katz [4] recently. While bodily exercise and generalized anoxemia may precipitate attacks in patients subject to anginal seizures—usually with rather characteristic alterations in the electrocardiogram, which are similar to those occurring in spontaneous attacks—Katz [4] has demonstrated that similar ischemic changes may be experimentally produced in normal persons without causing precordial pain, which observation leads this author to conclude that some other factor than ischemia plays an important rôle. In animal experiments Katz shows that: "Continuous pain can be produced in contracting skeletal muscle when the muscle is rendered ischemic"; that in the dog "Pain response was not due to the occlusion of the coronary artery, but to stimulation of afferent pain fibers located in the nerve plexus surrounding the vessels." He concludes: "The stimulus for pain appears to consist of some metabolic product produced quantitatively in proportion to the work done by the heart. The amount of the product produced is . . . increased when the heart works ineffi-

ciently, especially when the diastolic blood pressure is elevated, because the heart has to exert more effort in raising the pressure of its contents above the diastolic aortic pressure."

Evidence [5] derived from experimental arrest of the circulation of the human limb, carried out with and without associated effort, seems to justify the belief that whenever, in the presence of sclerosis or other coronary artery obstruction, the work of the heart is so increased that the demands upon the coronary circulation exceed the vessel capacity—anginal pain ensues. These experiments showed likewise that fatigued muscles failed to exhibit pain under similar conditions, suggesting an explanation for the clinical observation that the failing heart muscle is rarely associated with anginal attacks.

Thomas McCrae [6] challenged the idea that angina pectoris is always due to coronary disease and believed that we should regard this disease as one having a multiple etiology, including myocardial disease, viscero-sensory reflexes, and possibly purely neuro-psychic mechanisms. It is certain, at least, that extra-cardiac factors precipitate attacks. Early gastric lavage prevented attacks in one patient; in another prostatic treatment "cured" the angina. I have in mind also a man whose anginal attacks were relieved for a period of many months following a cholecystectomy; yet later he again suffered from angina and died in his second attack of coronary thrombosis.

In a very recent report [7] experimental and clinical evidence is presented in support of the statement that "Angina pectoris is due to acute, spasmodic, incoördinated contractions of the esophagus and stomach." Dr. Jackson's presentation of this subject at the Kansas City meeting of the American Medical Association was quite convincing, but corroboration must be forthcoming before such a novel theory can attract more than passing interest.

Warthin [8] taught that syphilis plays an important rôle in the causation of atherosclerosis, hence that coronary thrombosis and angina pectoris occur more frequently in syphilitics. To all of Warthin's students it was well known that he found evidence of syphilis where his contemporaries were unable to satisfy themselves as to its occurrence. Scott [9] also found one-half the cases of coronary artery disease dependent upon syphilis. Others do not find that syphilis predisposes to coronary sclerosis. Certainly present day teaching [10] does not stress syphilis as a cause of angina pectoris. The race in this country most extensively invaded by syphilis, the negro, shows a notable freedom from the anginal syndrome. Roberts [11] of Atlanta offers as an explanation of this fact that the negro "never worries very long about any one thing at any one time," and suggests that "the white man's burden is his nervous system." An English physician, Donnison,[12] who had a considerable experience in the Orient, stated that he had never seen angina pectoris in natives in Central Asia or China. An inquiry directed to a physician of 40 years' experience in India corroborates this observation. Wenckebach [13] noted as early as 1904 the marked difference in the incidence

of angina pectoris among a rural population as compared to that of the cities, but when he went to Vienna he observed a marked increase in these cases in his practice, and also that there was a further significant increase in the years of and after the War, which increase he attributed to worry and strain.

It is probable that the presence or absence of the anginal syndrome is to a considerable extent dependent upon the degree to which the nervous system of the individual is sensitive to various influences, physical and psychic, for it has been amply proved that extensive limitation of the coronary circulation may exist without pain or other evidence of the anginal syndrome. It may be assumed that such individuals have a high threshold of sensitivity to those influences which act as a "trigger mechanism" and set off the painful attack in susceptible individuals. There is some evidence that this "trigger mechanism" is associated with an endocrine imbalance, since adrenalin is known to precipitate attacks in individuals subject to angina and not in controls.

It appears that there is no constant toxic or degenerative etiology, and that angina pectoris must be looked upon as the result of a combination of reactions in the nervous and circulatory systems induced in certain individuals by the stress and strain of life. In general, angina pectoris is noted in the aggressive, head of the procession, stocky individual, rather than in the neuro-circulatory under-nourished type.

Until fairly recently angina pectoris was considered, if not definitely as a disease of the intelligentsia, certainly as a disease of the upper classes, but even this idea is losing ground. Many [10] doubt the importance of occupation. It has been pointed out [14] that while "occupation does not appear to play a significant part in determining those whose coronary arteries are affected by sclerosis—with respect to the occurrence of pain, however, occupation seems to be of real importance," and that pain occurs in a significantly higher percentage of housewives and manual laborers than in clerical, skilled workers and professional men. These conclusions are drawn from pathological records of the Presbyterian Hospital of New York City where the women occupying the ward beds are usually of the hard working class. Probably, records drawn from groups more fortunately situated may not agree on this point. It is notable that the former predominance of males is diminishing, probably due to entrance of women into the stress of industrial, business and professional life.

Several writers have suggested that the "heart mindedness" of the laity during the past two decades may play an important part in the apparent increase in the various manifestations of coronary artery disease. This may be a factor in the increased frequency of precordial pain, but it seems more probable that the mode of life of the past two generations has led to a progressive increase in vascular degeneration, especially of the coronary vessels—to quote Osler "in the make-up of the machine, bad material was used for the tubing," and with the increased strain of the past two decades

the " tubing " is inadequate to the strain. Most of us are aware of families showing this type of defective " tubing." But in the members of such families in whom we encounter pain as a presenting symptom, we will almost invariably find excess strain of some type as a precipitating cause of the painful attacks.

The mechanism of the pain production in these cases has been the subject of numerous essays; the majority favor the view that in some manner a transient ischemia of the heart muscle occurs. In occlusion of the artery, either slowly produced or by sudden thrombosis, there is no question as to the production of anoxemia, but whether in the paroxysmal transient attacks of precordial pain coronary spasm occurs is an unsettled question, although it seems the most reasonable explanation. That disturbed metabolism may be a factor in the induction of spasm is established by the work of Blumgart [15] and his associates. These authors have reported a significant number of instances of complete relief of pain in angina pectoris following total thyroidectomy. Beach [16] and others have noted similar relief following subtotal thyroidectomy. It is conceivable that a vagus pressure mechanism is present in some of these thyroid cases, but it is usually conceded that the lowering of metabolic rate, and hence of the circulatory demands of the body, is the basis of the improvement.

The question is often raised why heart pain is not felt in the heart. The answer entails an intimate knowledge of the visceral nerve supply. Ordinarily painful sensations do not arise in the heart; therefore, the brain is not accustomed to recognizing heart pain; hence when an adequate stimulus occurs the pain is frequently registered as from some other body area. The factor of spread of impulse has to be taken into consideration, since in many instances of excessive heart pain there is an overflow to adjacent areas. Less readily understood is the mechanism involved in those anginal cases in which the pain is first appreciated at some point well removed from the heart, whence it is transmitted to or towards the heart—a reverse radiation process.

Age at Which the Anginal Syndrome Appears

Most cases of angina occur after 50, but there is ample evidence that childhood and early adult life are not exempt. Heberden had one case at two years. There exist reports of a seven weeks infant [17] which died suddenly and at autopsy showed advanced degenerative coronary changes, and of a 13 year old girl whose left ventricle ruptured due to advanced coronary sclerosis. There is evidence [18] that coronary narrowing may be a sequel of acute rheumatic carditis and manifest itself as early as the second decade, and that these patients not infrequently suffer from severe and typical anginal pain. There are numerous instances in the third and fourth decades.

An associated study of importance in this connection is that of the pathology of coronary sclerosis.

Leary [19] has demonstrated this change as early as the third day of life, and finds it is "not rare in the first decade, more common in the second with fatal thrombosis in the third and later decades." He believes that "Atherosclerosis is a disease and not the inevitable consequence of age," and that it is due to a disturbance in the cholesterol metabolism.

Relationship between Angina Pectoris and Coronary Thrombosis

In patients with coronary artery disease angina is apt to follow strain, physical or emotional, whereas when coronary thrombosis occurs its onset is often while the patient is at rest. Certain instances of angina occurring during sleep may be the result of strain during a night-mare. Either type of seizure may occur with or following meals, a reflex effect that is not understood. Leuten [20] reports two instances of coronary thrombosis which followed closely upon the taking of a cold drink. In such cases there are two possibilities, a reflex coronary constriction with sequential thrombosis or a direct effect of cold upon the heart. Several workers have demonstrated changes in the T-wave of the electrocardiogram following the ingestion of cold water, but in these instances there was a considerable amount of water taken which may have caused an axis shift capable of producing similar changes in the T-wave.

Anginal seizures preceded the final occlusion in 22.4 per cent of 370 cases of coronary thrombosis, and in 45.1 per cent persisted or appeared after the occlusion.[21] These figures appear to disprove the earlier idea that anginal attacks are not observed following occlusion. It is probable that the temporary muscle failure sequential to the infarct causes the disappearance of the former painful attacks, but with recovery these may be renewed.

No attempt will be made to differentiate the type and reference of pain occurring in angina and in coronary thrombosis. The diagnosis rests in part upon the antecedent history, the occurrence of preceding similar attacks, especially in angina, and the presence or absence of a strain factor; but in each the immediate pain may be identical in type, in point of origin and in distribution. It is the sequence of events which tells one whether this attack is a recurrence of angina pectoris or a new situation to be dealt with—coronary thrombosis. Various authors have differentiated cases by the occurrence of high or low substernal pain and the reference of this pain to one or both arms. The writer is unable to make such a differentiation. Likewise, there is too often an absence of the crushing, tearing, agonizing pain of the classical textbook description. When this picture occurs diagnosis is made easier, but because in either angina pectoris or coronary thrombosis the pain may be mild or absent, or may originate at a point apparently not related to the heart, or may not be referred to either arm and even not transmitted beyond its point of origin—because of this variation in symptomatology, some consideration of those symptoms which may take the place of pain and their importance in diagnosis is in order.

Usually the anginal patient during the short attack remains quiet, rarely even moaning; there are no theatrics, as so often noted in the cardio-neurotic who complains of pain. After the attack is over he tells of his pain. The observer is keenly aware that momentarily the patient is in agony. While the attack is ordinarily immobilizing, that is, the patient "stops in his tracks," there are some who continue walking at a slower pace with relief. I have under my care at the present a man of 69 years who has frequent attacks (I have seen him in one severe seizure), and whose greatest relief comes with slowly pacing around his room. Wenckebach [22] compares this with "second wind," a physiological phenomenon of which we know remarkably little. Contrast both of the foregoing with the restless and panicky seizure associated with tobacco sensitiveness.

As a rule, the anginal attacks are of short duration—a few minutes, very rarely 15 to 30 minutes, a point of differentiation between angina pectoris and coronary thrombosis, for in the latter the pain continues until relieved by morphine, unless of the very mild or painless type. In both conditions the pain is uninterrupted, though there may be slight changes of intensity which are not dependent upon drugs. On the other hand, in the neuroses there is a notable variation in the intensity of the pain as described by the patient.

Dyspnea is not a common accompaniment of pain, though occasionally a paroxysmal dyspnea appears with the pain. In one reported case [23] the attacks could be averted by deep breathing.

In certain instances in which pain does not occur the patient may remain perfectly still during the attack and in every respect behave precisely like a patient experiencing the usual agonizing pain. Patients frequently experience in their seizures other symptoms in lieu of pain and such symptoms may be considered as equivalents of pain. According to Libman [24] these pain equivalents are more frequently noted in individuals who are hyposensitive to ordinary painful impressions. Not infrequently, in lieu of pain, dyspnea of an arresting type is experienced. This is sudden, paroxysmal, often nocturnal and accompanied by the classical sense of impending death, lasts during the attack and may disappear as suddenly as it appeared.

A similar clinical syndrome in which the dyspnea does not disappear may be due to a thrombotic closure of a coronary vessel.

I have seen several instances of coronary occlusion in which the predominating and initial feature was sudden dyspnea. Two seizures occurred by coincidence in a theater: In one a well known actor was forced by dyspnea to stop in the midst of his lines; in the second instance a woman of 50 years was seized with such sudden and urgent air hunger that she had to be carried from the theater. She had no pain at any time, but a terrifying dyspnea; yet she presented all of the usual signs of infarct, including a pericardial rub. Both of these cases showed unmistakable evidence of occlusion; neither had significant pain.

Profuse localized sweating may occur as an equivalent of pain. Such sweating should not be confused with that which commonly occurs with the shock of coronary thrombosis, nor with the less marked sweating of angina pectoris.

Palmer [25] reports a case of a physician of 61 years who, two weeks after an attack of precordial nocturnal pain, lasting one hour and requiring morphine, awoke to find the precordium, shoulder and left arm drenched with sweat; elsewhere no sweating. There was no pain, pressure or heaviness. He had had similar painful attacks two and six years previously. This case is reported as a case of angina pectoris.

Mackenzie notes local flushing and sweating with angina pectoris attacks. Vaquez notes fleeting vasomotor phenomena in angina pectoris. Osler [26] described one case in which profuse sweating preceded an attack of pain by one-half hour which, however, may have been an attack of coronary thrombosis with late pain. These changes represent reflexes from the heart or aorta to sweat glands, ciliary muscle or to end organs in the abdominal viscera.

A doctor of 67 years who, at the onset of his attacks had typical anginal seizures and later an occlusion, has during the past two years had attacks without pain initiated by marked salivation, nausea, and vomiting. If he stops at the onset of the attack, only the salivation occurs. After the attack he voids copiously. This has recurred frequently and over a long period and has not been associated with physical or electrocardiographic changes indicative of infarct. Save for the absence of pain and the symptoms described, the patient's sensations are those of his former anginal attacks.

Paroxysmal headache, vertigo, nausea and vomiting, and a sudden feeling of great weakness have all been described by reliable clinicians [27] as pain equivalents in angina. In some instances these appeared in the course of a classical angina as phenomena substituting the pain; in others they represented the presenting symptoms in a patient who was thought to be free from any cardiac complaints, yet died suddenly and showed at autopsy coronary or aortic disease without other cause for sudden death. It is probable that the vagus nerve plays a rôle in this confusing symptomatology. This nerve furnishes not only motor, but large sensory branches to both the gastrointestinal tract and the heart. In addition, there are numerous sympathetic pathways between these two systems. By either of these routes it is possible for pain or other symptoms to be registered as from a tissue in which it does not truly arise.

Relationship between the Symptoms of Coronary Disease and Congestive Heart Failure

Angina and heart failure are antagonistic conditions. The failing heart is incapable of causing the true anginal seizure. With the control of failure

with digitalis, the muscle may recover sufficiently to cause a return of the painful attacks which existed prior to decompensation. In failure, local anoxemia exists; the muscle performs inefficiently. Certainly disturbed metabolism of the heart muscle is present, but nothing comparable to the seizure of angina pectoris occurs unless coronary thrombosis develops. The most satisfactory explanation for this so far advanced is the fatigue anoxemia theory previously mentioned.

When occlusion occurs in the course of heart failure, if not immediately fatal, the symptoms characteristic of thrombosis may not appear at all. To the existing failure there is only an increase in already existent symptoms, often without any acute pain.

The Electrocardiogram in Coronary Disease

The changes in the standard lead electrocardiogram in coronary thrombosis are too well known to require more than passing comment. These changes in the R–S–T complex are initiated within a few hours of the onset, rarely returning to normal within six to twelve months, and there are permanent alterations in about 25 per cent of cases. As a rule, in addition to fusion of the R- and T-waves, there are distinct T-wave changes, generally some degree of inversion, but this is inconstant. Lead IV or some type of chest lead has offered some assistance both in diagnosis and prognosis, but with this technic normal variations introduce considerable confusion, perhaps more than in the case of the standard leads. Until cardiologists can agree as to a standard or standard chest leads, cardiographic diagnosis must rest upon the original standard leads. While the electrocardiogram is of great value in diagnosis in many instances, it must be admitted that exact correlation between the lesion and the electrocardiogram is impossible.

Because of the progressive changes which take place after an acute closure of one of the coronary vessels, the greatest amount of information will be derived from serial electrocardiograms, preferably taken daily. In this manner transitional changes will be shown, which would be missed in single records. This need for serial curves in cases of suspected acute occlusion is manifested by the fact that in rare instances tracings may remain normal or only slightly abnormal for several hours following occlusion, a point of importance in the differential diagnosis of coronary thrombosis and of acute surgical conditions in the abdomen. Hurxthal[28] warns against too great reliance upon the electrocardiogram in such instances. Furthermore, changes in the curves characteristic of infarct may be produced by myocardial ischemia brought on by a sudden myocardial insufficiency when the force is insufficient to drive the blood through narrowed or even normal coronary vessels; there is not acute closure of the vessel, but ischemia just as surely follows.

The serial changes described as characteristic of infarction take place in a fairly short space of time, ordinarily hours to days. Similar

changes developing more slowly are known to be associated with a myocardial fibrosis sequential to a chronic progressive coronary sclerosis; therefore, it is necessary to consider the time element in the interpretation of progressive changes in the R–S–T complex.

There are a few records of electrocardiograms during a spontaneous attack of angina pectoris [29] and several during induced attacks; in all of these the T-wave becomes flat or inverted and the S–T interval depressed.[4] In 75 per cent of 40 anginal patients similar changes followed effort, not necessarily associated with [30] pain. Experimentally induced anoxemia furnishes curves identical with the preceding, but these are transient, completely disappearing with adequate oxygenation.[31] It is probable, therefore, that myocardial ischemia is the immediate cause of these changes observed during attacks of angina pectoris.

In spite of all that has been stated regarding anoxemia as a cause of anginal pain and its association with coronary sclerosis, the fact remains that fully one-third of the patients with angina pectoris present entirely normal curves in the standard leads of the electrocardiogram. It seems probable that further observations with chest leads will show changes in this derivation, both in the patient with mild coronary sclerosis and in the one subject to anginal attacks. However, until this technic becomes standardized we must recognize that the electrocardiograph fails to detect about 33 per cent of the cases in this group.

Other Conditions in Which Paroxysmal Attacks of Precordial Pain May Occur

In many normal individuals hypochondriac or precordial pain or ache may follow effort. Usually this is low in origin,—probably never higher than the arm or shoulder. It is often lancinating, knife-like and of sudden on- and off-set. Due to the popular knowledge of sudden death in painful heart disease, there may be an associated anxiety suggesting the angor animi of angina pectoris, but rarely the compressions noted in angina pectoris. Not infrequently there is precordial tenderness associated with pains in this region which are not due to heart disease.

Esophageal or gastric distention may cause apical pain and may be relieved by belching or removing gas by the stomach tube.

Rhythmic or arrhythmic paroxysmal tachycardia may give rise to precordial pains of varying intensity. These are not usually of the type and severity which would cause confusion with angina pectoris; moreover, the patient clearly recognizes the sudden disturbance in rhythm, and it is not as a rule until this has continued for some time that pain is significant. The associated drop in blood pressure may so reduce the coronary flow that anoxemia develops. Rarely does the picture of shock appear until the attack has continued over many hours. I have seen recurrent precordial pain and tenderness in a boy of 17 years whose paroxysmal auricular tachycardia

returned each time digitalis in large doses was withdrawn. White [32] reports an exceptional case of bilateral anginoid pain severe enough to justify a consideration of alcohol injections, and four cases in which definite attacks of angina pectoris were brought on by paroxysmal auricular fibrillation or flutter.[33]

Certain patients who are found to have sclerosed coronary arteries exhibit pain of less sharp though paroxysmal character, due to intermittent ischemia. Rest and vasodilators furnish relief. These pains may show some radiation, but in none of this group are the associated symptoms of angina pectoris present. This syndrome may represent an early manifestation of angina pectoris, yet many of these patients (perhaps one-third) will, with proper management, show nothing more for years.

Experimental studies [5] indicate that anoxemia plus work results in pain in the muscle involved, an observation which seems adequately to explain the effort pain observed by the patient with coronary sclerosis. Not all cases of coronary sclerosis complain of pain; about 20 per cent develop an ultimate myocardial failure without pain at any period; the balance (80 per cent) complain of pain or dyspnea at some time. The pain in this group is characteristically a sense of fullness or pressure, like a constricting belt rather than an acute pain. It is usually substernal or precordial, and in only about one in ten does it show any significant radiation, and then more often to the epigastrium, when, if accompanied by nausea and vomiting, the impression of an acute indigestion is strengthened. Dyspnea may be suffocating and not at all associated with exertion; in fact, the dyspnea of coronary sclerosis is most frequently nocturnal. There are instances of relief from mild exertion. This type of pain is to be differentiated from angina in that it is not dependent upon effort, worry or cold, is less paroxysmal, and there is no associated and characteristic posture, some degree of dyspnea rarely being absent.

An easily differentiated type of precordial pain is that associated with advanced myocardial disease. Here the pain is rarely of the severe arresting type, is precordial and without radiation. This pain, the associated dyspnea and peripheral signs of failure, often clear under digitalis therapy.

In advanced valvular disease, especially stenosis of the mitral and aortic valves, paroxysmal pain may occur. In the first instance it is thought that the coronary vessels are collapsed following sudden increase in intra-auricular pressure; in the second, sudden drops in an already reduced pulse pressure lead likewise to a decreased coronary flow.

Mention has been made of disturbed thyroid function. In both hyperthyroidism and in the hypothyroidism of myxedema rather typical anginal symptoms may occur. Approaching diabetic coma and the hypoglycemia of insulin shock may be accompanied by such a painful picture. Not infrequently in profound anemias painful attacks occur which strongly suggest angina pectoris. In this condition the myocardial demands exceed the available oxygen supply and a transient myocardial anoxemia ensues.

Rupture of the aortic valve or of an aneurysm of either the thoracic or abdominal aorta may present the clinical picture of coronary thrombosis. In one such instance [34] an electrocardiogram characteristic of infarct was obtained, which may have been due to a relative myocardial ischemia without infarction.

The upper abdomen presents surgical emergencies which often are only with great difficulty and loss of time differentiated from acute coronary occlusion. Because the electrocardiogram is at times a bit tardy in presenting its evidence, it behooves one to weigh all clinical evidence carefully before denying surgery. An exploratory operation in the presence of an infarcted heart is no greater error than an unoperated ruptured ulcer.

Not all of these abdominal conditions which may become confused with angina are potential surgical emergencies. The sigmoid colon may give rise to transient pains which appear to arise in the precordium and may even radiate to the shoulder and arm. The associated anxiety state induces palpitation and arrhythmia, thus completing a cardiac picture.

An occasional source of confusion is a pulmonary artery embolism. The immediate signs and symptoms may be identical with those of coronary occlusion. If the left lower lobe is infarcted there will be in a short time an accompanying pleuritis which may overlie the pericardial sac. Here the initial symptoms, the fever, leukocytosis and the apparent pericardial rub, all point to the heart as the primary seat of trouble. If this occurs in a patient with evidence of peripheral varicose veins or phlebitis or after operation, the likelihood of embolus is strengthened. Fortunately, the early management of such cases is so nearly identical that a diagnostic error is not very serious.

Spontaneous pneumothorax may for a time be confused with occlusion, the resulting enfeebled heart sounds, signs of shock, and thoracic pain being readily attributed to the heart. About 25 years ago, even before we were as "coronary conscious" as at the present period, I saw such a condition in a man in his late thirties in whom, there being no antecedent pulmonary history, the heart was under suspicion until roentgen-ray showed a small anterior pneumothorax not demonstrable by physical means.

Another pulmonary condition which, according to Hamman,[35] is likely to be confused with coronary thrombosis is spontaneous interstitial emphysema. The sudden tearing of mediastinal tissue may produce severe pain, although I have observed two instances which occurred in the course of induced pneumothorax, which were not accompanied by any appreciable pain, though sufficient to lead to a widespread emphysema of the cervical tissues. Hamman describes a peculiar "crunching sound" with each heart beat which might be mistaken for a pericardial rub.

Aside from the painful seizures of angina pectoris, the only heart condition which should be confused with coronary thrombosis is the occasional instance of pericarditis, often pneumococcic in origin, in which the pain

comes on as suddenly as in coronary thrombosis and is very severe and may radiate to the arms. This may shortly be followed by evidence of myocardial insufficiency. Here the complete clinical picture of coronary thrombosis, pain, dyspnea, circulatory failure, collapse and eventual congestive heart failure, combined with a pericardial rub, may tax diagnostic powers. Added to this picture we have electrocardiographic changes due to pericarditis which may suggest occlusion. A differential point is that in pericarditis the rub is louder, over a greater area and more constant, while in cardiac infarct the rub when present is faint, usually transient and limited in the area over which it is heard. A demonstrable pericardial effusion is rare in cardiac infarct.

The pain of sub-deltoid bursitis may simulate that of coronary disease, and in cardiac infarct persistent shoulder pain may direct attention away from the heart. Mild or severe, burning, aching or wrenching pain in the shoulder region was encountered in 10 per cent of 14 survivals from coronary thrombosis.[36]

Disturbances of the spine and nerve roots presenting the radicular syndrome, when involving certain cervical and dorsal segments, may present a pain pattern very like that of true angina. These are commonly associated with postural defects and fatigue, and may be temporarily increased by anything which increases intra-spinal pressure, namely, coughing, straining, et cetera. Such phenomena as nausea, vomiting, and vasomotor changes, which are commonly associated with the pain of thoracic visceral disease, are not present in even the most extreme instances of root pain, and this pain is not relieved by nitrites.[37] A policy of " watchful waiting " in doubtful cases may relieve one of the embarrassment of changing the diagnosis of angina to one of herpes zoster, sciatica, lumbago or some other complication of spinal cord disease.

Diaphragmatic hernia has been confused with angina pectoris. In a recent report [38] a case of " diaphragmatic flutter " was described as simulating angina pectoris. The same patient subsequently came under my observation and will be the subject of an early report. This man entered the hospital with an admission diagnosis of angina pectoris, but was seen by me during an attack. That there was pain was evident, but here the patient was in constant motion and agitation and pounded his left precordium so violently it was thought that subsequent tenderness resulted therefrom.

This patient well illustrates the subject of false angina, the pseudo-angina of some writers, a term better discarded. As stated before the patient suffering from a true anginal seizure while in obvious distress is too concerned with the attack to wish or ask for sympathy, in fact, he is often remarkably quiet, while the subject of false angina presents exactly the opposite picture, his voluble description of his attack at once suggesting a neurotic background as a basis for his complaints.

The same type of patient complains of apical or precordial distress after

any psychic trauma: grief, worry, surprise, even extreme pleasure. Here the pain is rarely substernal or referred. These patients both in military and civil life demand considerable attention. They have been described under many names; probably neuro-circulatory asthenia or effort syndrome is the best.

There is another type of precordial pain which has been frequently classed with the neuroses and certainly presents the general picture of a neurosis, but which is truly toxic in origin. I refer to the dull ache, occasionally severe pain, noted by those who have become sensitized to tobacco, tea and coffee. This pain is rarely reflected, lasts for hours, but is not incapacitating; at no time does the patient appear ill. Complete withdrawal of the excitant is followed by complete relief; likewise, only slight exposure in those sensitized is sufficient to cause recurrence of the pain.

Differential Diagnosis

Concerning the differentiation of those non-cardiac, but true disease entities with which coronary artery disease may be confused, enough has been said. The anemias, hypoglycemias, valve and aortic ruptures, surgical abdomens, pulmonary conditions, and so forth, while a cause of temporary diagnostic embarrassment, are usually susceptible of differentiation after careful investigation, but after these are excluded there remain the larger numbers of either true instances of mild to severe cases of angina pectoris and coronary thrombosis, or a probably larger number of these cases of "false angina." Too great reliance cannot be placed upon the angor animi or sense of impending dissolution so strongly stressed by early writers. This is in part dependent upon the psychic pattern of the individual, although there is a peculiar indescribable sensation associated with some anginal seizures which is not entirely dependent upon the severity of the pain. As indicated before, probably the most conclusive evidence is the appearance of the patient during the attack. In angina pectoris it is a rare experience for the physician to observe the attack, and the description of the lay observer is not too dependable.

Standardized exercise tests which are both safe and yet sufficient to precipitate attacks of true angina pectoris have been introduced. These tests offer an opportunity for careful observation [39] during an attack brought on in the office or hospital, and for observations as to results of therapy. At least in those cases in which physical effort is the major factor, this method should prove a valuable means of differentiation from the false anginas.

The hysterical patient can with ease and abandon present for anyone interested an excellent simulation of an anginal attack. While it is true that organic heart disease may co-exist with a cardiac neurosis, this is not usually the case. In general, it may be stated that evidence of organic heart disease, as enlargement, enfeebled heart sounds (in absence of a pulmonary or pleural cause for the same), persistent hypertension, or any electrocardio-

graphic evidence of coronary vessel or heart muscle disease, is acceptable confirmatory evidence of coronary disease, angina pectoris, or thrombosis when the clinical aspects suggest one of these conditions. The converse unfortunately is not quite true in the case of angina pectoris, for more than occasionally one will encounter a patient with the typical anginal syndrome in whom there is no demonstrable clinical, roentgen-ray or electrocardiographic evidence of heart change. Rarely these patients die without ever presenting any further evidence. In this group the final opinion is only arrived at after the elimination of all other possibilities. Sometimes only a sudden death establishes proof of organic disease.

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ANGINA PECTORIS AND PERNICIOUS ANEMIA (OLD TERMINOLOGY), A RÉSUMÉ OF THE LITERATURE, WITH A CASE REPORT *

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HERRICK and Nuzum [1] in 1918, were the first to describe cases of pernicious anemia with symptoms of angina pectoris. They found four such in a group of 200 cases of primary anemias. Three of these patients died, one of anginal seizure. On none was a necropsy obtained. In 1927 Herrick [2] added two cases to his original group. He further stated that a very careful search of current literature during the previous nine years bore him out as to the relative infrequency of this syndrome.

Hunter,[3] Evans,[4] Sturgis,[5] Levine,[6] Conners,[7] Elliott,[8] Beach,[9] Smith,[10] Donald,[11] and Colvin [12] each told of but a single case, while others quoted from larger statistics. Reid [13] in 1923 reviewed the postmortem records of cases of pernicious anemia at the Boston City Hospital from 1916 to 1921 and found 11 cases which presented cardiac aspects. Bullrich [14, 15] of Buenos Aires has been widely quoted as having presented seven cases of this syndrome, but on a careful reading of his two papers, it would seem that only one of his cases might be pernicious anemia. Carey Coombs [16] in 1926 wrote that eight of 36 patients with pernicious anemia, all of whom he had personally observed, suffered from cardiac pain. Wilkinson [17] in a study of 370 cases of pernicious anemia found three cases with symptoms of angina or coronary thrombosis. Keefer and Resnik,[18] Porter,[19] Pickering and Wayne,[20] Hochrein and Matthes,[21] Paschkis,[22] Bloch,[23] Zimmerman,[24, 25] Reichel [26] in large series of pernicious anemia cases found comparatively few with anginal symptoms. There have been no cases of this syndrome at Harper Hospital in the past nine years and, in the anemia clinic in 1935, 43 cases of pernicious anemia were diagnosed and treated.

Herrick [1] in his first paper assumed that blood of poor quality going through somewhat narrowed coronary arteries might favor on slight provocation the development of an anginal attack. On observing patients with severe anemia he was frequently impressed with the remarkable degree of circulatory efficiency that was maintained. From this and other papers quoted, the consensus of opinion might be stated in the following quotation of Levine,[6] "Even with one-twelfth of the normal number of red blood cells, I do not believe that the anemia would initiate an attack of angina without some background of coronary disease." Many have reported improvement and often complete cessation of anginal attacks following transfusion, and, more recently, anti-anemia therapy. White [27] stated "although it is the anemia and not the heart trouble that has usually been responsible for death, congestive failure and angina pectoris have been seen in rare cases." Re-

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cently he told me he had seen a few cases with this syndrome and felt that the angina was due primarily to some coronary sclerosis or even spasm as described by Leary.

But on the other hand Cabot [28] wrote of three cases of intense and typical angina associated with pernicious anemia and without coronary change. One showed a moderate sclerosis, the others none. To quote him, "Such cases certainly make us skeptical of any etiology wholly on organic and permanent changes either in the coronaries or in the aorta." Willius and Giffin [29] reviewed the records of 1560 cases of pernicious anemia and found but 43 (2.7 per cent) with symptoms of angina. Their conclusions were that the anginal syndrome in pernicious anemia is due to anoxemia of the myocardium and not to coronary or aortic sclerosis.

Age and Sex

White [27] stated that men presented anginal symptoms three times as often as women and that three-quarters of the cases of angina were past 50 years. Lewis [30] gave 45 years as the average age, Zimmerman in his series found that women had angina more frequently than men, and that the average age of patients with angina was 57.3 years, while for patients who presented the syndrome of angina pectoris and pernicious anemia the average age was 60.1 years. Lee and Minot [31] stated that they had seen more men than women with pernicious anemia and that their ages ranged between 40 and 55 years. Schleicher [32] quoted 53.7 years as the average age of patients in his group of pernicious anemia.

Physiology

In 1922 Fahr and Ronzone [33] studied a case of pernicious anemia with a hemoglobin of 12 per cent, 1,560,000 erythrocytes, and an oxygen carrying capacity of only 2.2 c.c. per 100 c.c. of blood (normal is 5.5 c.c.). The minute volume of the blood was increased proportionately. There was no dyspnea, no cyanosis, no increased pulse rate, and a normal basal metabolism or rate of oxygen consumption. A necropsy revealed a dilated heart with moderate increase in the thickness of the ventricular musculature. Their conclusions were that in severe anemias, the increased minute volume, due largely to lowered blood viscosity was the outstanding compensatory mechanism for loss of oxygen carrying power of the blood. The pathologic changes in the heart muscle in pernicious anemia might well be due to lack of oxygen as the coronary circulation was taxed to the upper limit and was comparable to that in strenuous work. It is well recognized that profound circulatory changes may occur in anemia; Liljestrand and Stenström,[34] and Richards and Strauss [35] have shown that the cardiac output is increased in anemia; Dautrebande [36] found a 300 per cent increase in cardiac output at a hemoglobin concentration of 20 per cent, with a return to normal value when the hemoglobin concentration rose above 50 per cent. This he found

over several months as long as the hemoglobin was above 50 per cent Kisch [37] thought it was probable that a deficiency of the capillarization of the myocardium was an important factor in the development of the attacks of cardiac pain. Rothschild and Kissin [38] showed that in eight of 11 patients who suffered from angina pectoris, pain could be induced by breathing air deficient in oxygen and ascribed the pain to the direct effect on the myocardium. Dietrich and Schwiegk [39] thought that during an attack of angina pectoris there existed an ischemia of the cardiac muscle and that not only the changes in the electrocardiogram but also the pains were a result of this ischemia.

Lewis [40] from his experiments upon human voluntary muscle inferred that myocardial anoxemia was not the direct cause of anginal pain. He felt that such pain must have a physico-chemical basis and must be attributable to a change in the conditions in the tissue spaces outside the muscle fiber. On the basis of this view it follows that the avoidance of pain in muscle depends upon adequate irrigation with blood, which removes the pain-producing substance, thereby preventing its accumulation in sufficient amount to cause pain.

Although the reaction of heart rate and blood pressure to exercise is usually altered in anemia and such alterations may contribute to the development of anginal pains, it may be assumed that the precipitating factor in the production of anginal pain in anemia is the lack of oxygen, which acts by producing a physico-chemical state that is the concomitant of pain. The anemic patient may be stopped by one of four events—breathlessness, giddiness, angina, or intermittent claudication. If the coronary arteries are diseased the relevant event will be angina; if they are not, then it will probably be breathlessness or giddiness. But in some patients, for a reason that is not yet at all clear, breathlessness and giddiness seem to be less easily induced and exercise may be carried on to the point of producing angina pectoris even in the absence of local disease of the vessels.

Pathology

The most constant finding has been fatty degeneration of the myocardium. This change in the heart muscle is found in a variety of conditions and seems not to be inconsistent with perfect health. The fat is not due to a degeneration or breaking down of the muscle fibers, but is brought by the blood stream and deposited in the heart, and evidence is lacking that the myocardium is impaired thereby. In Reid's [13] cases enlargement of the heart of a degree that should be recognized clinically was not found; in six cases the actual weights of the hearts were between 240 and 340 grams, and in five between 300 and 400 grams. The hearts in this group of 11 necropsies showed the myocardium microscopically to be abnormal in only two cases. In these there were areas of necrosis of the fibers. In four instances the endocardium, especially on the papillary muscles, was mottled

and streaked with yellow, the so-called tigroid appearance. The epicardial fat was recorded as moderately increased in four cases and greatly so in two; otherwise these hearts were normal, save for moderate sclerosis of the coronary arteries in four, of the mitral valves in five and of the aortic cusps in two. Willius and Giffin [29] reported a necropsy on a woman of 55 with this syndrome. The heart was small and apparently normal except for fatty changes in the myocardium. Coombs [16] had one postmortem only; it showed a diffuse atheroma of the aorta. The coronary arteries were not mentioned. At necropsy Elliott [8] found in his case that the tigroid markings usually seen in cases of pernicious anemia were absent. By microscopic section there was no evidence of coronary or myocardial disease. Two of Reichel's [26] three patients came to necropsy. The heart of one had dilated chambers, normal aorta and valvular apparatus, and, microscopically, vacuolization of the muscle bundles. The second patient had arteriosclerosis of the aorta, fatty change of the left ventricle, and an area of myomalacia. The coronary arteries were not specifically mentioned in either instance but the finding of myomalacia in the second suggests the presence of coronary disease. Four cases in Zimmerman's [24, 25] series of pernicious anemia came to autopsy—two with angina and two without. All four showed the same thing—complete calcification of the coronaries. There are at least five cases described (Cabot,[28] Willius and Giffin,[29] and Elliott [8]) in which no changes in the coronary vessels were found postmortem.

Electrocardiograms

Pickering and Wayne [20] examined the electrocardiograms of 10 of their cases of severe anemia. In one with angina pectoris which persisted after cure of the anemia, there was a left ventricular preponderance. In two cases, the P–R interval was longer than normal when the patient was anemic and within normal limits after cure of the anemia. In the first case the P–R interval was 0.265 second when the hemoglobin content of the blood was 35 per cent and fell to 0.19 second when the hemoglobin content was 97 per cent. In the second case the corresponding figures were 0.205 second at a hemoglobin content of 38 per cent and 0.145 second at a hemoglobin content of 110 per cent. In the other cases no abnormality was noted during the anemic state. Curves taken immediately after the end of exercise in three anemic cases showed no changes in the shape of the R–T segment or any changes other than those directly attributable to exercise alone.

Reid [13] found the QRS–T interval of normal duration and concluded the increased output of the heart was not accomplished by a lengthening of the ventricular systole. On examining 20 tracings he found nothing that might be considered of diagnostic value or as peculiar to pernicious anemia. Porter [19] found in one case a slight left axis deviation and an isoelectric T-wave in Lead I. Reid,[13] Willius and Giffin,[29] Hochrein and Matthes,[21] Bloch,[23] and Smith [41] felt that there was no typical electrocardiographic picture.

Case Report

In May 1931, the patient, a male, 53 years of age, while at work suffered a severe, crushing, oppressive pain under the sternum. Previous to this he had experienced only an occasional mild attack. He was taken home and a physician was called who gave a small amount of digitalis, but no narcotic. The pain lasted about 24 hours, during which time the patient expectorated some pink sputum. Following this he remained in bed for two weeks and, after a few days' convalescence, returned to his work. For the next two months he was symptom free. Then he consulted another physician who treated him for diabetes although sugar was found in only one specimen. For one and a half years he had no severe attacks but everything he did was done with effort. His appetite was poor. During this period he was seen every two months by his physician.

In August 1933, the patient had a severe attack and another doctor was called. Following the immediate treatment he gave him hypodermic injections of iron and arsenic for anemia two to three times a week for eight months. From that time on he had frequent substernal pains. During February and March 1934 while working at night the patient had many severe attacks of pain radiating down both arms which never lasted more than 15 minutes. These attacks of pain came on at any time, after eating, or while sitting still, and were always accompanied by violent attacks of coughing. He also complained of frequency of urination. About this time nocturnal dyspnea began. In April 1934, his physician ordered an electrocardiogram which was reported as normal and hence he gave a favorable prognosis. Because of no improvement in his condition the patient sought another doctor and in August 1934 he had another electrocardiogram which showed left axis deviation and ventricular extrasystoles. For his pain he was never given nitroglycerine but always morphine sulphate by hypodermic injection which was invariably followed by nausea and vomiting. Still another physician saw him and suggested that he might have cancer.

The patient was first seen by the writer, following a severe attack of pain under the upper sternum September 15, 1934. A few additional items were added to his history. The pain even awakened him at night and frequently lasted for one and a half hours. It was very sharp, except occasionally when it diminished to a duller discomfort. Frequently it was located near the epigastrium and seemed to follow a rotary motion. Occasionally it spread out in oblong fashion and his arms pained terribly at the same time. Sometimes it was relieved by coffee.

Usually his bowels were regular. There had been some loss of weight, perhaps 20 pounds. Sometimes there was noted a slight edema of ankles and feet. He felt very weak, his appetite was poor, he ate no meat. He had been on digitalis and euphylline but had stopped taking them because of nausea.

He had never suffered with sore tongue, digestive disturbance, paresthesias, or anesthesias of fingers or toes.

The patient's past history was irrelevant except for a so-called attack of gall stones 11 years previous, with no recurrence. The patient denied venereal disease.

In the family history it was noted that his father had died at 64 "instantly, after working in field." One brother died of angina at 68. One sister, living, has angina at 69.

Physical Examination. The patient appeared moderately well-developed, poorly nourished, and much older than his stated age. His height was five feet six inches. His hair was streaked with gray, the skin was rather sallow, flabby, and somewhat dehydrated; the eyes showed an arcus senilis, and the sclerae were slightly yellow; the tongue was not noticeably smooth, the papillae were of moderate size.

The heart was definitely enlarged both to left and right. There was an accentuation of the first sound, a gallop rhythm, a systolic and a rumbling diastolic

murmur at the apex, and also a very loud diastolic murmur at the aortic area and along the left border of the sternum. The pulmonic second sound equaled the aortic second. The pulse was 84. There was noticeable pulsation of the neck vessels. Blood pressure was 120 over 50 millimeters of mercury. The liver and spleen were not felt. The knee jerks were active and equal.

Laboratory Findings. Urine examinations were essentially negative. The Kahn test was negative. Hemoglobin 53 per cent (Sahli); red blood cells 1,560,000 per cu. mm.; color index 1.7; mean diameter 8.3; white blood cells 4,500 per cu. mm.; stab polymorphonuclears 5 per cent; segmented polys 47 per cent; lymphocytes 41 per cent; eosinophiles 1 per cent; monocytes 5 per cent; basophiles 1 per cent. There were two 7 lobed polymorphonuclear neutrophiles, one 3 lobed eosinophile, and one nucleated red blood cell seen; marked anisocytosis, poikilocytosis, many slightly oval forms, some achromia, some cells well-filled with hemoglobin.

A diagnosis was made of hyperchromic macrocytic anemia, angina pectoris, and aortic regurgitation and stenosis.

Treatment. Because of marked dyspnea the patient was digitalized. He was also given euphylline grains 1½ three times a day, frequent high caloric feedings, nitroglycerine grains 1/150 as needed for pain, small amounts of whiskey and brandy, and two cubic centimeters of Parke Davis liver extract parenterally daily.

The patient had a bad cold twice, and because the increase of red blood cells seemed at times to be very slow, the liver extract was increased to four and for a short time to six cubic centimeters daily, as it is known that any factor, such as constipation, cold or infection, is enough to inhibit hematopoiesis. Once, following the injection of 6 c.c., the patient experienced bulging of his ear drums and stated that there was palpitation of his heart. He felt weak and had to lie down as soon as he reached home. The symptoms lasted but a very short time.

The patient was always able to relieve his substernal pain with nitroglycerine and after one week, when the red blood count had reached 2,450,000 and the hemoglobin 71 per cent, he rarely had an anginal attack unless he exerted himself more than normally. As will be noted the red blood cells reached 5,000,000 in a little less than three months.

Following the intravenous liver he took ventriculin and kept his red blood count at a normal level. He filled out, his weight increased 10 pounds, his appetite was tremendous, and his general well-being was that of a man on the road to recovery. But his heart always showed a very loud aortic diastolic murmur and to the end the aortic second sound remained louder than the pulmonic second. The patient had an occasional attack of cardiac asthma.

Because he felt so well, he returned to his work, which was very light, shortly after the first of January 1935. On the third day following his return to work, he had an unusually severe anginal seizure while carrying a very heavy bottle of water. Instead of dropping the bottle he held it while the attack lasted; this prevented his getting any nitroglycerine. From then on he went slowly down hill. His cardiac asthmatic attacks became almost continuous. He had an idiosyncrasy for morphine and pantopon, manifested by marked nausea and vomiting, but was definitely relieved from his cardiac asthmatic attacks, without after-effects, by dilaudid given hypodermically and occasionally by sodium bromide and chloral hydrate by rectum.

As his cardiac asthma increased in frequency until it was almost continuous, his anginal attacks almost ceased. At the same time his appetite decreased and he was unable to continue with ventriculin. He began to show edema of lungs, abdomen, and feet which finally reached his knees. This was relieved by frequent intravenous injections of 2 c.c. of salyrgan. He became semi-comatose March 22, 1935, and two days later died in his sleep.

Autopsy. Permission to examine the heart only was given. The findings were

as follows: Weight 760 grams; left ventricular wall 27 millimeters; right ventricular wall 12 millimeters. Grossly there were well marked fatty areas in the myocardium and a "tiger lily" appearance, especially of the papillary muscles. There was functional insufficiency of all valves. No signs of cardiac infarction either old or recent were found. The aorta and the aortic valve showed marked sclerosis and calcification, and the cusps could not approximate. The openings to the coronary arteries were enlarged, but on cross section through the arteries themselves they were found solidly calcified, barely admitting the tip of a common pin.

Summary

A case of angina pectoris and hyperchromic macrocytic anemia (with aortic stenosis and regurgitation, coronary sclerosis, cardiac asthma, and an idiosyncrasy for morphine) has been presented with a résumé of the literature bearing particularly on this symptom complex. It apparently is not a common syndrome. The anginal pains were relieved as usual with nitroglycerine but were less frequent when the blood picture approximated the normal, or at least, improved when a higher blood count was obtained. The theory has been propounded that anoxemia is a factor initiating angina, and it is conceivable that, in pernicious anemia, blood of poor quality might readily aid in the development, on slight provocation, of an anginal spell. Because the age period of both of these diseases is approximately the same it may be a natural occurrence that they are found together in the same patient. It was felt by one investigator that patients with anemia do not very often develop angina because of their general easy fatigue which causes them to stop short of the danger point. But as most patients with pernicious anemia do not have angina, the anemia per se cannot be a primary cause.

Again the pathologic changes in the heart muscle in pernicious anemia have been thought to be due to lack of oxygen from the fact that the coronary circulation is taxed to the upper limit, comparable to the effects of strenuous work. In general the consensus of opinion has been that there were no diagnostic abnormalities in the electrocardiograms and what changes were noted could be traced to a coincident cardiosclerosis.

Conclusions

The writer presents a case of angina pectoris with pernicious anemia and reviews the slightly over one hundred similar cases in the literature. As so few cases of this syndrome have failed to show sclerosis of the coronary arteries, one may safely assume that most anginal pains in this symptom-complex result from anoxemia of the myocardium due to sclerosed coronary arteries. But when in addition the blood is deficient in adequate oxygen carrying power, the functional capacity of the myocardium is still further diminished and angina occurs more readily. Hence the incidence of cardiac pain in cardiosclerosis with pernicious anemia is higher than in cardiosclerosis alone.

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BODILY BUILD AND HEREDITY IN CORONARY THROMBOSIS *

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THE importance of habitus in its association with certain pathologic states has been the subject of considerable discussion in recent years. The coexistence of obesity and hypertension has often been emphasized. It has been our clinical impression that many individuals who have coronary thrombosis are overweight, but no adequate statistics are available regarding this question. The tendency for abnormal degrees of arteriosclerosis and their premature manifestation to occur with unusual regularity in certain families, and the proclivity of angina pectoris to be a familial disease have been recognized for many years.

To investigate the importance of bodily build and heredity in coronary thrombosis, 300 cases observed in the past few years at The Mayo Clinic have been reviewed. The diagnosis of coronary thrombosis was confirmed in these cases by postmortem findings, characteristic changes in the electrocardiogram, or a typical history of this condition at some time prior to our examination plus residual electrocardiographic changes. This group of individuals consisted of 272 men and 28 women who were between 40 and 80 years of age; 118, or 39 per cent of these patients, were between the ages of 50 and 59 years. In each case the following data were obtained: age, height, average weight prior to the patient's admission to the clinic, weight at the time of examination, detailed characteristics of bodily build whenever stated, and family history, including, whenever possible, the age and cause of death of parents and siblings. The presence or absence of cardiovascular renal disease in the family was noted.

Having obtained the present weight of each individual, this was compared with the average weight for the age and height, as given by the insurance standards. The weight of each individual has been expressed as a percentage difference from the standard weight according to sex, age and height. Figure 1 shows the distribution of weights expressed in these terms for the entire group studied, using the observed weight of the individual at the time of his examination at the Clinic. The mean deviation was + 1.8 per cent. The weight varied from — 42.5 per cent of standard to + 47.5 per cent. The number of patients who were overweight slightly exceeded those who were underweight; 51 (17 per cent) were more than 15 per cent overweight, while 39 (13 per cent) were more than 15 per cent underweight. The weight of 13 patients exceeded the average weight by more than 30 per cent, while the weight of only one was more than 30 per cent less than the average

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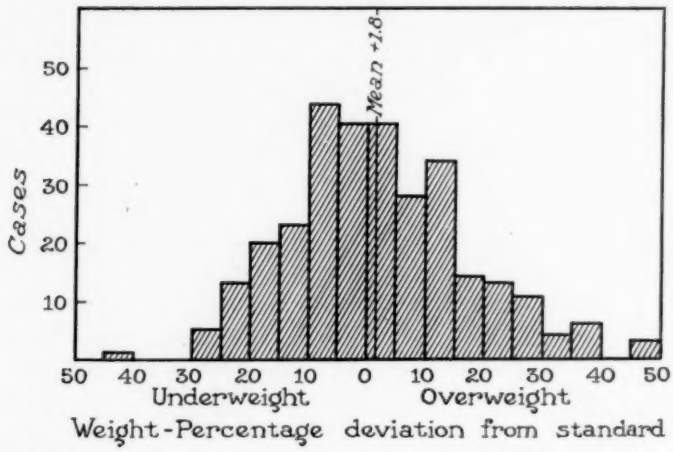

FIG. 1. Distribution of weights of patients at time of examination at the Clinic, expressed in terms of deviation from standard weight according to sex, age and height.

weight. As previously stated, the weights used in plotting the graph in figure 1 were those determined at the time of examination at the Clinic. Many patients were very ill and had lost weight. It seemed appropriate to use the average weight of the patient prior to his illness instead of the weight as determined at the time of examination, and to compare the former with the standard weight. The results of this study are shown in figure 2. The

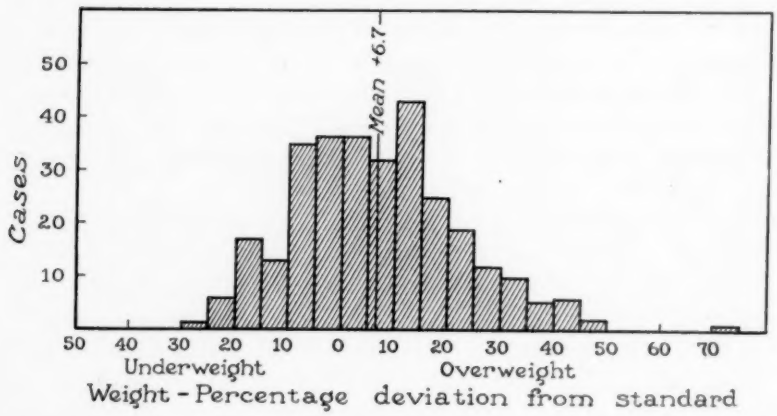

FIG. 2. Distribution of weights of patients before illness, expressed in terms of deviation from standard weight according to sex, age and height.

mean deviation from the average was in this instance + 6.7 per cent. Only seven individuals gave a history of an average weight 20 per cent or more below the standard, while 55 individuals had an average weight of more than 20 per cent above the average. Thirty-seven individuals (12 per cent) were more than 10 per cent underweight while 123 individuals (41 per cent) were more than 10 per cent overweight, as determined by the standards used.

Figure 3 gives a more detailed analysis of the problem; the total group of women and the men in each age group were studied separately, except the five patients who were between 30 and 39 years of age, who were too

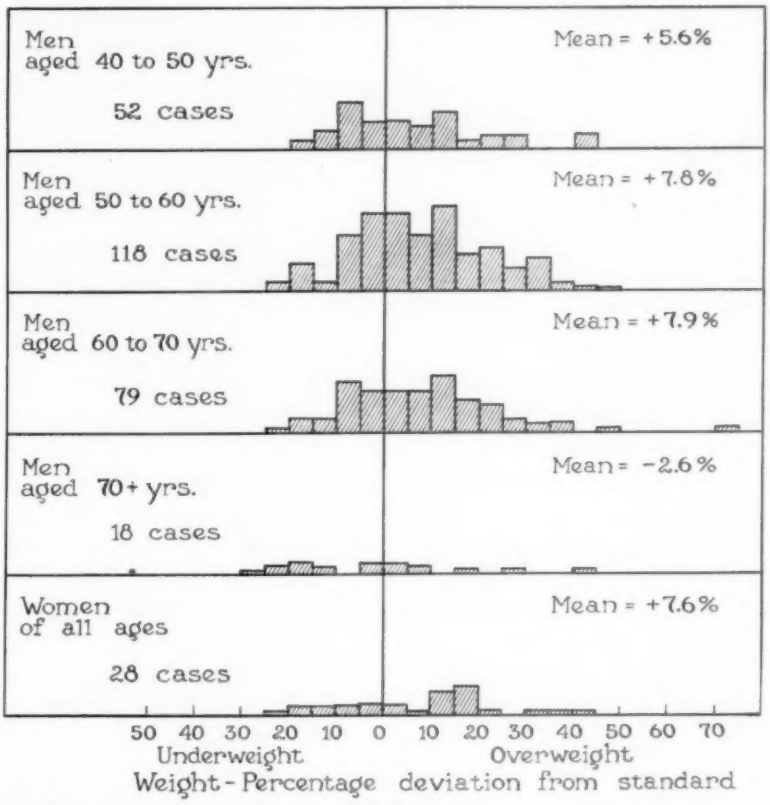

FIG. 3. Distribution of weights of patients before illness, expressed in terms of deviation from standard weight for men and women separately and for specific ages for the men.

few to be significant. The weight used was that which the individual described as his normal average weight prior to the onset of the presenting illness. The tendency to overweight is evident among patients of all ages, except among the men who were more than 70 years of age. The findings obtained in this last group are probably partly the result of inadequate standards for this age. The men who were between 50 and 70 years of age and all of the women showed a mean deviation of more than + 7.5 per cent from the average.

Details of habitus, aside from a tendency to obesity, were meager. A number of individuals were described as plethoric; some were of the short, stocky type and had thick necks; others were of large powerful build. A ruddy complexion or flushed face was often noted, as was the fact that the individuals were often nervous and high-strung. In contrast to this, a num-

ber of persons were obviously very ill, pale, sallow, or cyanotic, and revealed evidence of recent loss of weight. Apparently all types of bodily build were represented and the data were inadequate to determine statistically the predominance of any one type.

There was a family history of cardiovascular renal disease in 165 (55 per cent) of the 300 cases. Fifty-seven (35 per cent) of the patients said that two or more members of their immediate family (parents or siblings) had some type of cardiovascular disease. Eighteen patients said that both parents had died of heart disease or cerebral hemorrhage. The cause of death of one of the parents, or the cause of the death of siblings, was given as cerebral hemorrhage in 52, coronary thrombosis in 14, heart disease (type not stated) in 52, hypertension in five, dropsy in nine, nephritis in 23, and uremia in three cases, respectively. It seemed of interest to determine whether individuals who gave family histories of cardiovascular disease died at an earlier age than did their parents. Such data were available in 88 cases. In 70 cases, only one parent had died of this type of disease. It was discovered that 30 patients died at a younger age and 12 at a more advanced age than had the affected parent, while 28 were still living but had not yet attained the age at which the parent had died. In the 18 cases in which both parents had succumbed to cardiovascular disease, three patients died at a younger age than had either parent, seven died at a younger age than had one parent, six, who are still living, have not attained the age reached by the parents, and in two cases the age at which death of the parents occurred was unknown.

In the series of 165 cases in which there was a history of cardiovascular renal disease among other members of the family, 83 of the patients have died. The average age of the patients at the time of death was 59.2 years. Of the 135 patients who did not give any history of cardiovascular disease in the family, 50 have died; their average age at the time of death was 60.1 years. No conclusive information is gleaned from these figures as in both groups of cases the age of the patients at the time of death was apparently the same, although fewer deaths occurred in the group in which there was no family history of cardiovascular renal disease. The evidence presented suggests that the presence of cardiovascular disease in the family diminishes the chances of longevity. The high familial incidence of cardiovascular renal disease in this series of cases supports the view that there is an hereditary tendency for these pathologic conditions to develop.

In this group of 300 cases, there were 83 patients (28 per cent) who had hypertension. It was thought that the habitus in this group might differ from that of the group in which the patients did not have high blood pressure. Table 1 shows that in this series the weight of 59 per cent of the patients who had hypertension was at least 5 per cent more than the average weight for height and age according to the standards used, while only 48.85

per cent of those who did not have hypertension were more than 5 per cent overweight. Similarly, the group of patients who had hypertension included only 16 per cent of patients who were more than 5 per cent underweight, while the group of patients who did not have hypertension included 27 per cent of patients who were more than 5 per cent underweight. It is thus evident that the patients who had hypertension were inclined to be more obese than were those who had a normal blood pressure.

TABLE I

Relation of Weight of Patient to Family History and Value for the Blood Pressure

	Patients	Percentage of patients who were more than 5 per cent underweight	Percentage of patients whose weight was normal (+5 pounds to −5 pounds)	Percentage of patients who were more than 5 per cent overweight
Family history of cardiovascular disease	165	23.03	24.84	52.13
No family history of cardiovascular disease	135	25.19	23.70	51.11
Hypertension present	83	15.66	25.30	59.04
Normal value for blood pressure	217	27.19	23.96	48.85

Table 1 also shows the percentage of individuals who were overweight or underweight and who did or did not give a family history of cardiovascular disease. Slightly more than 50 per cent of the patients in both groups were overweight by 5 per cent or more, as compared to the standards.

COMMENT

While the habitus of the patient does not appear to be of outstanding importance in the predisposition to coronary thrombosis, the occurrence of overweight in more than half of the cases is not without significance. This observation, moreover, is another indictment against obesity in general.

The data in this study do not permit the determination of conclusive facts regarding the hereditary tendencies to coronary disease, although the more than casual repetition of cardiovascular renal diseases in certain families is of interest and undoubtedly is of importance. The fact that it is virtually impossible to obtain reliable data regarding the causes of death, even among the patient's grandparents, to say nothing of preceding ancestors, makes the establishment of a hereditary continuity almost impossible, except in rare instances.

Nevertheless, clinical contacts with many patients over long periods of time create an impression that hereditary influences play a much more important rôle in coronary disease than is generally admitted.

Summary

A study of the habitus of 300 individuals who had coronary thrombosis revealed a mean deviation of +6.7 per cent from the average weight for height and age. The individuals who had hypertension tended to be more overweight than did those who had a normal blood pressure. There was a family history of cardiovascular renal disease in 165 of the 300 cases. Familial predisposition to cardiovascular disease showed no correlation with the degree of obesity.

THE EFFECTIVENESS OF TRICHLORETHYLENE IN PREVENTING ATTACKS OF ANGINA PECTORIS *

By William S. Love, Jr., M.D., F.A.C.P., *Baltimore, Maryland*

Trichlorethylene has been used for some time in the treatment of trigeminal neuralgia. Its therapeutic activity in regard to this condition has been discussed by Glaser,[1, 2] and an extensive bibliography of its use for this purpose is given in his papers. It has also been used as an anodyne in dental procedures and for dental pain[3, 4] and with some success as an anesthetic for operations upon the face.[5] In a conversation with Dr. David Bryce in which the discussion turned upon angina pectoris, it was suggested by him that trichlorethylene might prove of use in preventing such attacks. The following investigations were then undertaken.

Certain Pharmacological Actions of Trichlorethylene

After exhibition of this preparation had apparently benefited certain patients with angina pectoris, Dr. John C. Krantz, Jr., of the Department of Pharmacology of the University of Maryland, kindly undertook the study of certain questions in regard to the pharmacological action of this drug.[6, 7, 8] His observations indicate that

1. Trichlorethylene causes a constriction of the perfused vessels of the frog.
2. It does not influence the oxygen consumption of rats.
3. It has an irregular effect upon the coronary flow of the dog, at times increasing and at times diminishing this flow.
4. It decreases the blood pressure and slows the heart rate in dogs.
5. When applied directly to the sciatic nerve it fails to block the blood pressure and respiratory responses to faradization.

He concludes that the drug probably causes hypalgesia by depressing the basal ganglia and perhaps produces a relaxation of the vessels of the splanchnic area while causing a peripheral vasoconstriction.

Pharmacological Actions of Trichlorethylene on Human Subjects. In 27 patients with cardiovascular disease of some type, under treatment with this drug, there were 13 with systolic blood pressures of over 150 mm. of mercury and diastolic levels of over 100. In this group of hypertensive patients, taking trichlorethylene by inhalation in 1 c.c. doses thrice daily, the systolic pressure fell from 20 to 30 mm. in four, and 40 or more mm. in two. The shortest period in which such a drop is known to have occurred

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The author is indebted to the Calco Chemical Company, Bound Brook, New Jersey, for supplying much of the trichlorethylene used in carrying out this investigation.

is one week, the longest six weeks. One patient showed a rise of 10 mm. The systolic pressure fell 20 mm. in one patient not classified as hypertensive. Three normal individuals with normal blood pressures inhaled 1 c.c. thrice daily for three weeks. In two of these there was no significant change in the blood pressure. One consistently had an average fall of 20 mm. in systolic and diastolic pressure, beginning during the inhalation and lasting for about 20 minutes. There was no permanent lowering of the pressure in this individual. Thus in 31 individuals subjected to the inhalation of 1 c.c. of trichlorethylene three times daily, there was an immediate and transient fall in blood pressure in only one, and in seven a significant fall occurring a week or longer after the inhalations were begun. It is probably of significance that six of these seven individuals suffered from hypertension, and that six of thirteen hypertensives presented such a reaction.

The following experiment indicates that such decreases in blood pressure are not associated with any marked impairment in the conductivity of reflex pathways.

W. M., aged 48 (case 24), known hypertensive for at least three years. Blood pressure at beginning of treatment, 190/130; two weeks later, 175/105; six weeks after initiation of treatment, 130/85.

Blood Pressure before test	Left hand immersed in ice water Blood Pressure in		
	30 seconds	1 min.	2 min.
135/85	170/100	190/110	210/140

Skin temperatures have been determined by a thermopyle before, immediately after, and after continued inhalation of trichlorethylene in three normal individuals. In two there has been no change in temperature and in one there has been a slight drop. This suggests that in the dosage used there occurs neither a marked peripheral vasodilator nor vasoconstrictor response to trichlorethylene in man.

There is not sufficient evidence at this time upon which to base an explanation of a reduction in blood pressure following the continued use of trichlorethylene. It is perhaps due to the sedative action of the drug.

The pulse rate has not been significantly altered in most individuals. A few have shown a transient rise of as much as 20 beats per minute. This is contrary to the results obtained by Krantz and his co-workers on dogs and is probably to be attributed to psychic reactions.

Toxicology

Joachimoglu [9] considered the drug harmless. Krantz and his co-workers [8] conclude that repeated anesthetizing of rats did not markedly influence their growth curves or subsequently lead to important pathological changes in their viscera. Eichert [10] reports two cases of toxic psychoses following therapeutic use of trichlorethylene and quotes from Zulkis one of addiction to the drug with toxic effects. In all three cases gross overdosage had been

voluntarily taken by the patients. All recovered without demonstrable ill after-effects. Taylor [11] reports that following daily six hour inhalation exposures to trichlorethylene, rats survived six months when concentrations of 0.2 per cent or lower were used. Pathological examination at the end of the experimental period revealed no signs of degeneration in any organ. A concentration of 0.3 per cent proved too high, only two of six rats surviving six months.

No evidence of toxicity has occurred in any of the 28 cases of this series. One patient has been taking trichlorethylene from time to time for three years, and during the first year used it almost daily.

Alice Hamilton [12] discusses 284 cases of industrial poisoning supposedly due to trichlorethylene. In this group there were 26 deaths. While there is no decisive evidence on this point, it seems likely that such cases of industrial poisoning are due to substances other than pure trichlorethylene. Trichlorethylene on contact with air and light may form decomposition products among which phosgene has been identified.

Method of Treatment

While some observations have been made upon the usefulness of this drug in relieving immediate attacks of angina pectoris and the pain of coronary thrombosis, the primary purpose has been to discover if anginal seizures would be prevented or diminished in frequency and severity by this drug.

Twenty-seven patients have been treated as follows: from two to four, usually three, inhalations of trichlorethylene have been given daily. Sealed frangible glass ampoules of one cubic centimeter are crushed in a handkerchief. The first inhalation has always been taken in the presence of a physician so that the immediate effect might be noted, and the patient reassured, if alarmed. Thereafter, patients are advised to take the drug either while reclining or sitting in an easy chair, for marked lightheadedness often occurs, and occasionally there is a brief loss of consciousness. The treatment is continued as above for three weeks. If no therapeutic effect has been achieved in this time, the use of trichlorethylene has been discontinued, and the method considered ineffective. Should the treatment prove effective, the number of inhalations is reduced in each individual to the minimum consistent with an adequate relief of symptoms.

The Effects Produced by the Inhalation of One c.c. of Trichlorethylene Thrice Daily, other than upon Cardiac Pain

When inhaled this drug is irritating to the mucous membranes of the respiratory tract, and a sensation of burning commonly occurs in the nose, and the patient usually coughs, but not violently. Within a few seconds after the inhalation is started the patient complains of lightheadedness and

in about one-half this effect is marked. Such lightheadedness lasts only a few moments and leaves the patient mentally clear. Three patients of 27 lost consciousness for periods lasting from two to five minutes. Headaches subsequent to its use have not been noted. Five patients described a feeling of marked well-being, amounting to a mild euphoria. When the patient has been nervous and irritable and sleep has been restless, well-marked sedation, loss of irritability and quiet sleep have usually followed the exhibition of this drug. This, however, has not been accompanied by any dulling of the mentality of sufficient degree to be noticed by the patients or manifested by any loss of ability to perform their usual work. One patient became so alarmed at temporary loss of consciousness that this mode of therapy had to be discontinued.

Effect of Trichlorethylene Upon the Pain Accompanying Coronary Thrombosis

Six patients have been given trichlorethylene during immediate attacks of pain due to coronary thrombosis. Cases 1, 2 and 3 received the drug within 12 hours of the onset of such pain, and case 4 had been started the preceding day in the hope of preventing paroxysms of hypertension associated with anginal pain. In this last case thrombosis occurred after three inhalations. The patient lived for three days and trichlorethylene had no appreciable effect upon the pain. Cases 1 and 2 received immediate relief from pain. In case 1 the intervals between recurrence of pain were very irregular, and if additional trichlorethylene were inhaled at the beginning of the pain it was aborted within a few minutes. Case 2 lost consciousness for about five minutes after each inhalation, and freedom from pain was obtained for about one hour. Morphine proved more satisfactory for controlling pain in this patient who died on the seventh day of her illness. Case 3 received no relief with morphia in ½ grain doses given twice before admission to the hospital. A single inhalation of trichlorethylene gave marked relief in a few minutes and the inhalation was immediately repeated, complete relief from pain being then obtained. Freedom from pain lasted from one-half to three-quarters of an hour, and it did not again become intense for about three hours. Inhalations were ordered for this patient at three hourly intervals and he was permitted to receive additional inhalations on request. After 72 hours only occasional inhalations were taken.

Cases 5 and 6 were seen five and seven days respectively after coronary thrombosis had occurred. As noted in the case histories, striking relief followed the exhibition of trichlorethylene to both of these patients. However, it is well known that the pain and distress of coronary thrombosis tend gradually to become ameliorated at varying times after their onset. One could not say in case 5 that this had not happened in the natural course of events. Case 6 offers more positive evidence of the rôle played by trichlorethylene in as much as morphine had previously failed to give relief up to

the moment the inhalations were started. In less than 12 hours after the initial inhalation this patient had his first restful night and sleep.

Thus in three of four cases seen within 12 hours of the onset of coronary thrombosis trichlorethylene afforded relief from pain, proving more useful than morphia in one case and less so in one case. In case 1 morphia was not used. In one case trichlorethylene was ineffective. In two more cases relief of pain followed the exhibition of this drug but because of the length of time elapsing from the occurrence of the thrombosis to the initiation of inhalation treatment, disappearance of the pain cannot with certainty be attributed to this treatment. It is possible that trichlorethylene was more effective than morphia in one of these cases. When successfully used, it had the advantage over morphia of not causing constipation.

Case 1. White male, aged 54. Hypertensive arteriosclerotic cardiovascular disease. Angina pectoris followed in six months by coronary thrombosis. Continued frequent recurrence of pain, severe, while in bed. Blood pressure very variable; before attack averaged 200 millimeters of mercury systolic and 120 diastolic; after attack fell to 140 systolic and 100 diastolic, then rose to 180 systolic and 120 diastolic with paroxysmal elevations as high as 260 systolic and 160 diastolic. Slight relief with theobromine. Pain often aborted by single inhalation of trichlorethylene, and inhalations given three times a day prevented pain. The blood pressure became stabilized at about 175 systolic and 110 diastolic. The patient has been under observation two years, during which time there have been two apoplectic seizures. Cardiac pain recurs periodically and is relieved and prevented by trichlorethylene. Electrocardiogram just before attack of thrombosis: Leads I and II show the coronary type curve; a record 16 months later shows no essential difference. This patient is a very high strung, irritable individual.

Case 2. White female, aged 49. Coronary thrombosis. Blood pressure, 90 systolic and 70 diastolic. Died on seventh day. Trichlorethylene gave temporary relief lasting for about one hour after each inhalation. This patient was unconscious for about five minutes after each inhalation. Morphia proved more satisfactory in this case.

Case 3. White male, aged 48. Acute coronary thrombosis preceded by anginal pain on exertion for four days. Leads I and chest lead type of acute coronary curve. Blood pressure on admission, 150 systolic and 110 diastolic, dropping to 80 systolic and 60 diastolic. Pain not relieved by morphia. Relieved by trichlorethylene completely for one-half hour after inhalation and pain ameliorated up to two or three hours.

Case 4. White male, aged 50. Arteriosclerotic cardiovascular disease. Paroxysmal hypertension with anginal pain. Coronary thrombosis—died third day after onset. Blood pressure 120 systolic and 95 diastolic, going to 180 systolic and 120 diastolic in attacks. Electrocardiogram before attack: Normal mechanism. Trichlorethylene started day before thrombosis and continued to death. No relief.

Case 5. White male, aged 52. Arteriosclerotic cardiovascular disease. Coronary thrombosis with pain persisting in attacks for one week while in bed. Blood pressure, 110 systolic and 80 diastolic. Electrocardiogram: none. Complete relief in 24 hours.

Case 6. White male, aged 71. Arteriosclerotic cardiovascular disease. Coronary thrombosis with persistent pain, nausea and vomiting; complete incapacity five days after attack. Blood pressure, 120 systolic and 90 diastolic (stated to have previously averaged 170 systolic and 100 diastolic). Complete relief of pain within

12 hours after exhibition of trichlorethylene; restful sleep. Morphia in 1/8 grain doses had previously failed to give relief. Trichlorethylene continued one week; no recurrence of pain after drug stopped.

Trichlorethylene Used to Prevent Attacks of Angina Pectoris

Of the remaining 21 patients, 18 had either arteriosclerosis or arteriosclerosis and hypertension combined; there was one case of syphilitic aortitis, one case of chronic nephritis, and one case in which there was a history of hypertension not found at time of examination. Of these patients nine gave a history of having had an attack of coronary thrombosis not more than two years previously. The electrocardiogram was normal in one, of the coronary type in 10, presented definite deviations from normal in nine and was not recorded in one. All of the above patients presented angina pectoris as a symptom of their disease. Trichlorethylene was inhaled by these patients as a rule three times a day. In these 21 patients anginal seizures were prevented completely by the inhalations in eight; they were definitely diminished in frequency and severity in eight and moderately diminished in one. This last patient had syphilitic aortic insufficiency and was receiving antiluetic treatment. This of course may account for the improvement that was observed. Four patients received no benefit from the inhalations. In seven patients it was noted that the pain recurred as severely as formerly whenever the inhalations were discontinued, the period of time elapsing before its recurrence varying from 24 hours to several weeks. The period of time from the initiation of treatment to the cessation of symptoms varied considerably, no attacks occurring in some instances after the first inhalation, and in others the improvement being gradual—case 25 did not achieve his maximum improvement until six weeks after beginning the inhalations. In one patient * this treatment gradually lost its effect as a preventative in two months, but still could be effectively used to relieve immediate severe attacks of angina pectoris.

The exercise tolerance of these patients has only been directly tested in case 26. In this case it will be noted that there was a definite increase in the amount of exercise performed without pain. The pain, however, was just as severe when it was finally induced. All patients receiving benefit from the treatment could do more of ordinary activities than was possible before it was commenced, and where such statements are definite, they are noted in the case histories.

I have no data for an adequate comparison of the effectiveness of trichlorethylene with that of other drugs used for the relief of angina pectoris. The above studies have been directed toward determining its effectiveness in preventing such attacks. However, it has been noted to be effective for

* Since offering these observations for publication, case 23 has reported that prevention of attacks no longer results from inhalation of trichlorethylene, and that he has had to retire from business because of their frequent occurrence when under mental strain. Therefore there are two patients who have reported that the original beneficial effect of trichlorethylene inhalations did not last.

the former purpose in several cases in which other drugs have been used. Thus in case 20 amyl nitrite had at first afforded relief from pain, but later failed to do so; inhalations of trichlorethylene were then found effective.

Five patients other than those with coronary thrombosis obtained immediate relief from anginal seizures; three specifically note that no relief was obtained. However, it is my present impression that there is little likelihood of this drug proving as effective for the relief of the anginal attack as are other already accepted methods of treatment.

There is no evidence that this drug in any way effects a cure; symptoms usually return when its use is discontinued.

Cases of Angina Pectoris

Case 7. White male, aged 37. Neurotic personality. Anginal type of pain, tight, retrosternal, radiating to left arm, occurring on unusual exertion or after large meals. Blood pressure, 150 systolic and 105 diastolic. Electrocardiogram: slurring of QRS, T_1 inversion, large Q_3. Pain prevented by theobromine, which also caused vertigo and nausea. Trichlorethylene prevented attacks, none occurring after third day of taking drug. The pain recurred whenever the drug was discontinued. Blood pressure after trichlorethylene, 130 systolic and 90 diastolic. Under observation one year. Died of pneumonia.

Case 8. White male, aged 47. Hypertensive cardiovascular disease. Coronary thrombosis one month previously. Continued severe attacks of anginal type of pain while in bed. Blood pressure, 170 systolic and 120 diastolic. Electrocardiogram: Leads I and II type coronary curve. Complete incapacity. No relief from theobromine. Complete prevention of pain by trichlorethylene, the pain recurring when drug discontinued. Patient under observation three years and in the last 12 months has resumed his occupation, which requires much walking. Blood pressure after taking trichlorethylene, 140 systolic and 100 diastolic, and has remained at about this level. At the present time the patient has an occasional sensation of oppression behind the sternum and a single inhalation of trichlorethylene will promptly relieve this.

Case 9. White male, aged 60. Hypertensive arteriosclerotic cardiovascular disease. Two weeks previously there had been an attack diagnosed as acute coronary thrombosis. Continued attacks of severe precordial pain at times radiated to left arm, occurring while in bed. Blood pressure before attack, 190 systolic; immediately after, 130; for week preceding examination by me, 170; at time of examination, 200 systolic and 100 diastolic. Electrocardiogram: none. Trichlorethylene completely prevented the pain; pain returned when drug was discontinued. This patient later took inhalations for the immediate relief of anginal attacks with success. Blood pressure from 185 systolic and 100 diastolic to 200 systolic and 110 diastolic. Patient living two years later, occasional pain; no regular medication.

Case 10. White male, aged 61. Hypertensive arteriosclerotic cardiovascular disease of two years' known duration. Angina pectoris of one year's duration. Eight months ago diagnosed coronary thrombosis. At time of examination doing office work several hours daily; very slight exertion caused constricting pain behind sternum radiating to both arms. Blood pressure, 260 systolic and 130 diastolic. Electrocardiogram: Left axis deviation, T_2 and T_3 inversion. During the first two weeks of taking trichlorethylene there occurred only one attack of mild pain. Patient was walking eight blocks without difficulty. Blood pressure, 200 systolic and 110 diastolic. Two months later at full work, but occasional heavy sensation over precordium. Trichlorethylene discontinued. At present patient takes occasional

courses of theocalcin. Trichlorethylene in single inhalations failed to influence immediate seizures. There is now a severe arteriosclerotic retinitis with visual impairment.

Case 11. White male, aged 64. Diabetes mellitus, arteriosclerotic cardiovascular disease, angina pectoris. Blood pressure, 160 systolic and 110 diastolic. Electrocardiogram: T_1 and T_2 inversion, arched ST segments. Pain occurs on walking a little rapidly, or on going up moderate hills, at times after meals. The blood pressure remained about the same after taking trichlorethylene. There was greatly increased but not complete freedom from pain while taking this drug, and the pain would recur several days after the drug was discontinued. This patient was followed four months.

Case 12. White male, aged 53. Diabetes mellitus, arteriosclerotic cardiovascular disease. Anginal pain occurring if patient walked four blocks. Blood pressure, 140 systolic and 100 diastolic and remained at this figure after trichlorethylene was used. There was complete prevention of pain. This patient was treated with trichlorethylene for only one month because of expense of treatment. Pain recurred after trichlorethylene was discontinued. Electrocardiogram normal.

Case 13. White male, aged 56. Diabetes mellitus, arteriosclerotic cardiovascular disease. Anginal pain produced by moderate exertion. Blood pressure, 150 systolic and 100 diastolic and not affected by trichlorethylene, which also did not affect the pain during three weeks treatment. Electrocardiogram: left axis deviation.

Case 14. White male, aged 43. Hypertensive cardiovascular disease, neurotic type personality. Anginal type of pain, moderate exertion causing pain. Electrocardiogram: left axis deviation, slurring of QRS waves. Blood pressure, 160 systolic and 120 diastolic. Blood pressure after trichlorethylene, 135 systolic and 95 diastolic. Theobromine derivatives gave this patient no relief. There was complete absence of pain while taking trichlorethylene, and the pain recurred when the drug was discontinued and the blood pressure returned to 150 systolic and 110 diastolic.

Case 15. White male, aged 38. Coronary thrombosis two years previously. Blood pressure, 120 systolic and 80 diastolic. Electrocardiogram at time of occlusion: acute coronary curve, Lead II and Lead III type. Curve, two years later, large Q_2 and Q_3, slurring of QRS and T_3 inversion. This patient had a heavy feeling of pressure behind the sternum on walking as little as a block or on going up one flight of stairs. This feeling completely disappeared while taking trichlorethylene three times daily, and the patient resumed his occupation at the end of three weeks. On reducing the trichlorethylene to once daily the pain returned but not as frequently as formerly. On again taking the drug three times daily there was no pain. He has changed his occupation to one of considerable mental strain, and short periods of great activity; discomfort does not occur as long as trichlorethylene is taken.

Case 16. White male, aged 59. Hypertensive arteriosclerotic cardiovascular disease. Anginal pain on moderate exertion; able to carry on occupation as insurance adjuster without great difficulty. Blood pressure, 178 systolic and 120 diastolic. Electrocardiogram: Lead II and Lead III type coronary curve. No relief from immediate attacks on exhibition of trichlorethylene and attacks not lessened in frequency and severity in two weeks' trial. He refused to take this drug longer. The blood pressure was not affected. The patient obtained moderate relief with theocalcin. Patient died 20 months later, from coronary thrombosis.

Case 17. White male, aged 40. Gives history of hypertension, but this was not found at examination. Anginal type of pain, of moderate severity, not incapacitating. Blood pressure, 140 systolic and 100 diastolic. Electrocardiogram: Left axis deviation. Complete prevention of pain with trichlorethylene. Neurotic personality. No history available after one month.

Case 18. White male, aged 55. Arteriosclerotic cardiovascular disease. One

year previously this patient had had an attack of severe precordial pain radiating out the left arm and lasting 48 hours. He was kept in bed for six weeks. During this time an electrocardiogram revealed low voltage, slurring of QRS waves, T_2 and T_3 inversion. An electrocardiogram six months later showed only T_3 inversion and low voltage. There had been several minor attacks preceding the severe one. Following the major attack the patient had frequent attacks daily, occurring with anger, excitement or exertion, and more severe in cold weather. At time of examination the blood pressure was 120 systolic and 80 diastolic. Electrocardiogram: Low voltage, otherwise normal mechanism. Complete relief in 24 hours after starting inhalations of trichlorethylene. There was no effect upon blood pressure. Patient under observation for six months at time of writing; only occasional attacks of mild pain. This patient was very high-strung and irritable and he has noted a marked diminution in this irritability since taking trichlorethylene. It has been inhaled three times daily throughout the period of observation.

Case 19. Colored male, aged 41. Syphilitic aortitis, aortic insufficiency, angina pectoris. Blood pressure, 140 systolic and 60 diastolic. Trichlorethylene lessened the severity and frequency of pain to a moderate degree during a month's treatment. The patient was receiving antiluetic treatment. Electrocardiogram: Left axis deviation.

Case 20. White male, aged 56. Arteriosclerotic cardiovascular disease. Coronary thrombosis five months before examination. Total disability because of recurring anginal pain on slight exertion or excitement. Blood pressure, 220 systolic and 140 diastolic. Immediate attacks at first had been relieved by amyl nitrite, which caused severe headache. Trichlorethylene prevented attacks for two months and then lost this effect, but it continued to afford relief in immediate attacks of pain. Electrocardiogram: Lead II and Lead III type of coronary curve.

Case 21. White male, aged 54. Arteriosclerotic cardiovascular disease. History of coronary thrombosis two years previously; since that time retrosternal oppression on exertion or excitement. Blood pressure, 150 systolic and 90 diastolic. Lead I and chest lead type of coronary curve. Theobromine gave no relief. Trichlorethylene prevented such pain for a period of one month. No observations since this time. No effect upon blood pressure.

Case 22. White male, aged 76. Arteriosclerotic cardiovascular disease. Electrocardiogram: Left axis deviation; slurring of QRS. Infected gangrene of right foot. Paroxysmal pains of anginal type occurring while in bed and persisting after amputation. Relieved by amyl nitrite. Blood pressure, 150 systolic and 100 diastolic. Frequency and severity of pain markedly diminished while taking trichlorethylene both before and after amputation. No change in blood pressure.

Case 23. White male, aged 68. Arteriosclerotic cardiovascular disease, angina pectoris. Crushing precordial pain caused by exertion or excitement; relieved by nitroglycerine. Nitroglycerine caused severe headache. Blood pressure, 150 systolic and 105 diastolic. Two weeks after trichlorethylene, blood pressure 130 systolic and 80 diastolic; no pain since drug started. Six months later at work, occasional pain, much less severe than formerly. Continues to take trichlorethylene daily. Electrocardiogram: left axis deviation (see footnote on page 1192).

Case 24. White male, aged 48. Hypertensive arteriosclerotic cardiovascular disease, angina pectoris. Squeezing, vice-like, retrosternal pain radiating out left arm, occurring only on exertion. Known hypertensive for several years. Blood pressure, 190 systolic and 130 diastolic. Pain occurred on walking rapidly for two blocks. Electrocardiogram: slurring of QRS waves, convex ST_2, inverted T_2. Blood pressure two weeks after trichlorethylene, 175 systolic and 105 diastolic. Estimated 20 per cent improvement. Six weeks after trichlorethylene, blood pressure, 130 systolic and 85 diastolic; could walk 10 blocks rapidly. Four months later could

walk 20 blocks without pain; blood pressure, 128 systolic and 80 diastolic. Trichlorethylene discontinued. Returned in three weeks with blood pressure 140 systolic and 100 diastolic and occasional return of pain. Again the pain was prevented by trichlorethylene inhaled three times daily and patient continues to take this drug, varying the frequency of inhalation from one to three times daily according to the return of pain.

Case 25. White male, aged 76. Arteriosclerotic hypertensive cardiovascular disease, angina pectoris. Heavy oppression in chest on slight exertion such as walking one-half block up slight grade. Relieved by amyl nitrite, but this drug caused headache. Trichlorethylene failed to relieve immediate attacks of pain. Blood pressure, 170 systolic and 105 diastolic. Electrocardiogram: Left axis deviation, slurring of QRS waves. Trichlorethylene used for two weeks, discontinued because it produced unconsciousness at times and this caused the patient great anxiety. There had been no effect upon the pain. Blood pressure at the time of the drug's discontinuance 180 systolic and 110 diastolic.

Case 26. White male, aged 57. Chronic nephritis, tumor of urinary bladder, generalized arteriosclerosis, angina pectoris, uremia. Anginal pain of one year's duration. At time of initiation of treatment pain was caused by the slightest exertion such as getting out of bed. Trichlorethylene, one ampoule by inhalation thrice daily. In one week he was able to be up and move about ward. At this time exercise tolerance over standard portable steps equaled two round trips. At end of second week he was able to make seven or eight round trips. Electrocardiogram: Left axis deviation. Patient died, uremic coma, at end of third week. Anatomical diagnosis: chronic cystitis, bilateral chronic nephritis, generalized arteriosclerosis, coronary sclerosis, fibrosis of apex of right ventricle, fulguration necrosis of bladder wall.

Case 27. White male, aged 50. Arteriosclerotic cardiovascular disease, angina pectoris. One year previously this patient had suffered from a coronary occlusion. The electrocardiogram at that time was of the Lead I, chest lead type of acute coronary occlusion curve. Following the above illness the patient never was able to return to his occupation of executive because of recurring seizures of angina pectoris. Five weeks before death the patient became bedridden, precordial pain occurring in severe seizures while at rest. Theobromine derivatives were of help in diminishing the frequency and severity of attacks. The patient was given inhalations of trichlorethylene three times daily and inhalations for immediate attacks over a period of three weeks without appreciable benefit. Nitroglycerine failed to relieve the pain. He died in a prolonged attack of pain during which the electrocardiogram revealed a Lead III type of acute coronary curve.

I can offer no adequate explanation of why this drug is effective in preventing attacks of angina pectoris. The fall in blood pressure at times noted may be a factor in some cases, but obviously cannot explain the greater number of cases in which no such reaction has taken place. No constant effect upon coronary circulation has been shown to occur. There is no evidence that conduction of nerve impulses is impaired. There is definite evidence that this drug has sedative and anesthetic properties. A few unrelated observations have been made upon pain due to other causes, and in the cases so treated a sedative and hypalgesic action has been noted. In the case histories it is frequently stated that the patients are of high-strung, nervous temperament. The hypalgesic and sedative action of this drug is the only explanation of its effectiveness in preventing and relieving angina pectoris with any evidence in its favor at this time.

Summary and Conclusions

1. The inhalation from two to four times daily of ampoules of trichlorethylene, containing 1 c.c., has been used with some success in the prevention of attacks of angina pectoris. However, this series is not sufficiently large to warrant too favorable conclusions, since in any small series there may be a considerable distortion due to the element of chance.

2. While pure trichlorethylene in the recommended dosage does not seem to be toxic, nevertheless, because of the reported cases of industrial poisoning due to this agent, it should be used with some caution.

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CASE REPORTS

TREATMENT OF HEMOLYTIC STREPTOCOCCIC MENINGITIS WITH PARA-AMINO-BENZENE-SULFONAMIDE; REPORT OF A CASE, WITH RECOVERY *

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The observations of European investigators and more recently of Long [1, 2] and Schwentker [3] in this country on the treatment of beta hemolytic streptococcic infections by para-amino-benzene-sulfonamide suggested to the author the use of this drug in infections of the central nervous system. The opportunity presented itself to try this drug on a case of fulminating meningitis following a middle ear and mastoid infection admitted to the Neurosurgical Service of Dr. Charles Bagley, Jr., at the University of Maryland Hospital on December 18, 1936. The dosage used in the treatment of this case was the same as that used by Schwentker [3] in a similar case treated by him several weeks previously. It seems worthwhile to make this preliminary report of a single case because of the striking therapeutic results. The rapid recovery of a patient suffering from a disease which is practically always fatal strongly suggests that the treatment employed may have had a specific effect.

Case Report

History. On December 5, 1936, the patient, a white female 28 years of age, began to have earache in the right ear. Later that evening the ear began to discharge followed by some relief from pain, but the pain continued somewhat until about December 12. From December 12 to December 17 she seemed much improved. On December 16 she went to bed feeling quite well, but was awakened at 3:00 a.m. with severe headache. By morning she had become very confused and drowsy. Her father stated he was "unable to get anything out of her." Her family physician took her to the Frederick City Hospital on December 17 where she was seen by Dr. A. A. Pearre. There a diagnosis of meningitis was made clinically and examination of the cerebrospinal fluid on December 17 showed 3880 cells with 79 per cent polymorphonuclears. No bacteria were seen in the smear. Examination of the blood revealed a white cell count of 29,600. The following morning she was admitted to the Neurosurgical Service of Dr. Charles Bagley, Jr., at the University Hospital. While the patient was being transferred from Frederick to Baltimore, Dr. Pearre called and stated that the spinal fluid culture taken the day before was positive for *Streptococcus hemolyticus*. The past history was negative.

Examination. On admission the patient appeared critically ill. The skin was flushed and hot. She was unresponsive and reacted only to painful stimuli. There was a yellowish watery discharge from the right ear. No swelling over mastoid or ear. Divergent strabismus. Deep reflexes equal and hyperactive. Kernig positive.

* Presented before the Neuropsychiatric Section of the Baltimore City Medical Society, January 14, 1937.

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Abdominals diminished. Bilateral plantar extensor response. Rigidity of neck with mild opisthotonos. Hearing reduced in left ear (since childhood). Peripheral facial paralysis on right side.

On December 22, 1936, the examination of the blood was as follows: Hemoglobin 100 per cent; r.b.c. 4,400,000; w.b.c. 5600; polymorphonuclears 89 per cent, lymphocytes 10 per cent, large mononuclears 1 per cent. Blood non-protein nitrogen 27 mg. per cent, blood sugar 114 mg. per cent. Wassermann reaction negative. On December 26 the white blood cells were 20,000; polymorphonuclears 88 per cent; lymphocytes 10 per cent; large mononuclears 2 per cent. Sedimentation rate 34 mm. in one hour. On January 5, 1937, the white blood count was 11,000. The blood culture of December 18, 1936, was negative after five days. A smear of the pus taken from the ear on December 19 revealed pus cells, polymorphonuclears predominating, together with gram-positive diplococci and streptococci. A culture of this pus showed *Staphylococcus aureus*. Urine examinations were entirely negative on December 26, January 1, and January 6. The findings in the spinal fluid are cited below.

Course. On admission to the hospital the patient was very stuporous. The temperature was 105.4° F. (R). A mastoid infection was considered likely because of the peripheral facial paralysis, but it seemed useless to consider operation. Examination of the spinal fluid in the Frederick City Hospital on December 17, 1936, had shown a pleocytosis of 3880 cells per cu. mm. and a positive culture for hemolytic streptococci. Immediately upon admission late in the afternoon of December 18, the spinal fluid was found to be cloudy, contained 5181 cells, and was under a pressure of 333 mm. of water. The next morning the culture from this fluid showed a heavy growth of beta hemolytic streptococci. In the afternoon of December 19, a second puncture was done and the fluid was found to be under a pressure of 440 mm. of water. Twenty-five cubic centimeters of fluid were withdrawn and 20 c.c. of 0.8 per cent para-amino-benzene-sulfonamide in normal saline solution were injected intraspinally. Following this a subcutaneous injection of 200 c.c. of the same drug was given. Treatment was continued from this point on as described in a later section and summarized in table 1.

On December 20, twenty-four hours following the administration of the drug, the temperature dropped to 104° F. and there was a striking decrease in the spinal fluid cell count from 5181 to 1026. The pressure also dropped from 440 to 240 mm. of water. The patient was able to take fluids by mouth, smiled occasionally, but was still drowsy and disoriented. Once or twice she inquired about her surroundings, but late in the evening she again became very unresponsive.

On December 21, the temperature dropped to 102° F. (R) and the patient seemed slightly improved. In the afternoon she became more confused and resistive. She muttered to herself frequently. The spinal fluid pressure was 110 mm. of water, contained 1134 cells, and the culture was still positive for *Streptococcus hemolyticus*.

On December 22 she refused food. She became moderately cyanotic and the respiratory rate increased to 40. She was very noisy and cried out frequently. The spinal fluid pressure was 90 and the cell count dropped to 600. In previous cultures the organisms grew out overnight, but the culture taken on this day showed a very sparse growth in 36 hours.

On December 23, she was more coöperative but was still mildly disoriented. The temperature dropped to 99.4° F. (R). A bloody tap was obtained on doing the spinal puncture. A smear was made from the fluid and showed a few gram-positive cocci, but the culture was sterile. A transfusion of 300 c.c. of blood was given without reaction. The respiratory rate continued around 40. At no time during her course had there been swelling over the mastoid process, but in view of the general improvement, it was felt wise to consider doing a mastoidectomy. Roentgen-ray of the mastoids was done and Dr. H. J. Walton reported "moderate clouding of

TABLE I

Chart Showing Cerebrospinal Fluid Findings and Record of Treatment

Day of disease	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18	19	20	22	28
Day of month	(Dec.) 17	18	19	20	21	22	23	24	25	26	27	28	29	30	(Jan.) 1	2	3	5	11
Cerebrospinal Fluid Cell count	3880	5181	—	1026	1134	600	Bloody tap	—	450	325	385	309	78	80	79	75	—	37	40
Culture	Positive	Positive	—	Positive	Positive	Sparse growth	Smear pos. no growth	—	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	—	Negative	Negative
Pressure (mm. of H_2O)		330	440	240	110	90	—	110	300	118	200	220	195	175	140	110	—	175	155
Treatment (para-amino-benzene-sulfonamide) *Oral* (gm.)					6	6	6	4	4	4	4	4	4	4	4	4	4	—	—
Subcutaneous (0.8% solution) (c.c.)			200	350					—	—	—	—	—	—	—	—	—	—	—
Intraspinal (0.8% solution) (c.c.)			20	35	15	35	18	35	20	28	25	—	—	—	—	—	—	—	—

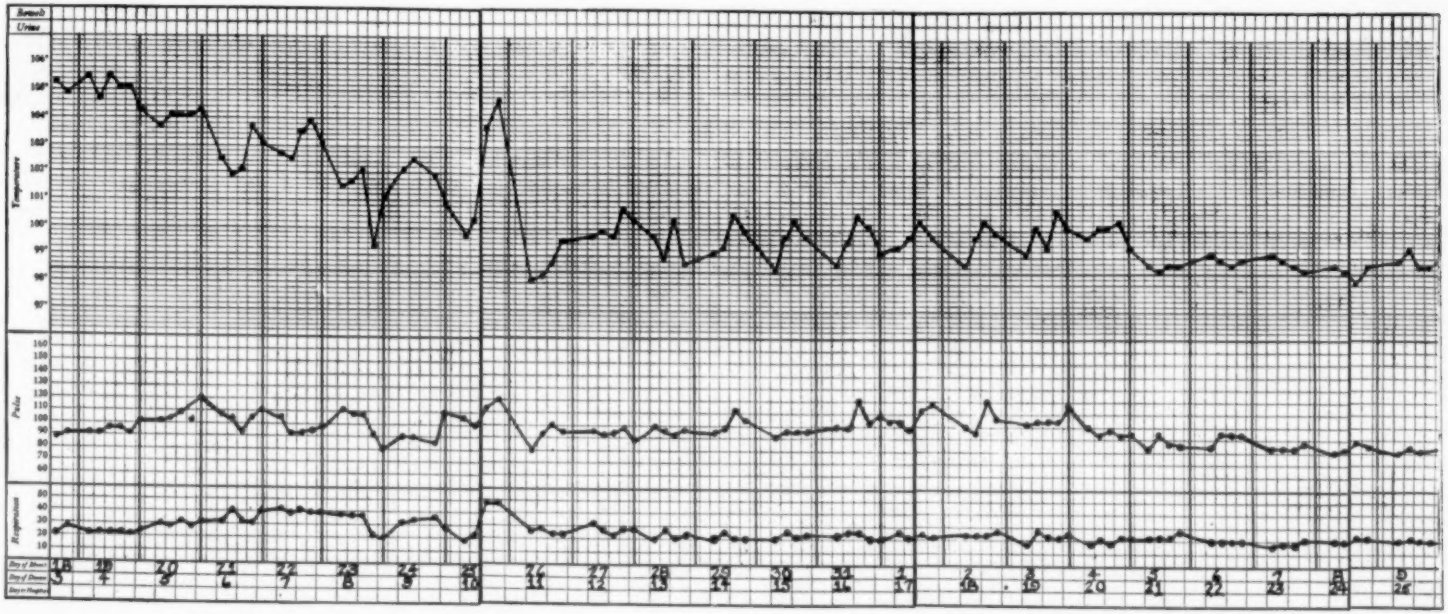

Chart of the temperature, pulse and respiration during the course of hemolytic streptococcic meningitis.

the cells in the right mastoid process, suggestive of an infection. There is no indication of breaking down of the cell partitions." His impression was "mastoiditis, probably acute."

On December 24, the temperature again rose to 102.4° F. (R). In the afternoon Dr. E. A. Looper did a right semi-radical mastoidectomy. The mastoid was found to be necrotic and filled with pus. The mastoid cells were curetted and the antrum opened widely. The ossicles and drum were removed. The dura was exposed above and the lateral sinus below. The patient stood the procedure well. It is of great interest to note that the spinal fluid had become sterile on the previous day.

On the following morning, December 25, the temperature dropped to 99.6° F. Her condition was definitely improved. She was more alert and talked with visitors. In the afternoon a second transfusion of 300 c.c. was given. She had a reaction following this and the temperature rose to 104.6° F. (R). The right ear and mastoid were draining profusely. The spinal fluid cell count was 450, pressure 300 (patient struggling), and culture of the spinal fluid was negative. Slight cyanosis of the skin was still present.

On December 26, her color was improved and respirations were slower. She was able to feed herself, talked coherently, and was definitely more alert mentally. She talked with her visitors and seemed cheerful. The temperature dropped to 98.4° F. (M) and the cell count to 325.

From this time on her improvement was steady. Between December 26 and January 4, the temperature ranged between 98.4° F. (M) and 100.6° F. (M). The medication was discontinued on January 3, and on January 5 the temperature dropped to a normal level. Between January 5 and January 12 the temperature rose to 100° F. (M) on two occasions. The cell count dropped to 40 on January 11. Ten consecutive cultures of the spinal fluid were sterile. Since January 8, she has been allowed out of bed.

Examination on January 11 showed her to be bright and mentally alert. Her father could see no change in her mental acuity. The peripheral facial paralysis on the right side noted on admission was still present. The deep reflexes were all hyperactive, with bilateral ankle clonus. The plantar responses were equivocal. The fundi were normal.

Treatment. Between December 19, 1936, and December 27 the patient received nine intraspinal injections of 0.8 per cent para-amino-benzene-sulfonamide in amounts ranging from 20 to 35 c.c., depending upon the amount of fluid withdrawn. On December 19 and 20, respectively, 200 c.c. (1.6 gm.) and 350 c.c. (2.8 gm.) of 0.8 per cent para-amino-benzene-sulfonamide were injected subcutaneously.

On December 21, 22, and 23, 6 gm. of the substance were given in the form of "Prontylin" tablets by mouth, 3 tablets six times a day. From December 24 to January 3 she was given 4 gm. every 24 hours, or 3 tablets four times a day.

As yet the optimum dosage of this drug * in the treatment of beta hemolytic streptococcic infections is undetermined. Long feels that large doses should be given in the first few days of treatment. He has found that patients tolerate a dose of 1 gm. per 20 lb. of body weight every 24 hours for as long as a month. He has pointed out that the drug administered orally should be given in divided doses over a 24-hour period.

In this case, four intraspinal injections were given after the spinal fluid became

* The crystalline para-amino-benzene-sulfonamide used was made by the Du Pont Chemical Company, and the "Prontylin" tablets by the Winthrop Chemical Company. Two derivatives of para-amino-benzene-sulfonamide are on the market under the name of "Prontosil" solution and "Prontosil" tablets. Prontosil solution may be used for subcutaneous injections but not intraspinally, for Schwentker [3] has found that Prontosil solution increases the cellular reaction in the leptomeninges and is therefore more irritating than solutions of para-amino-benzene-sulfonamide. For further discussion of these derivatives the reader is referred to Long's paper.[1]

sterile, and the drug was continued by mouth for 11 days after obtaining a sterile spinal fluid.

In the preparation of the powdered para-amino-benzene-sulfonamide for parenteral and intraspinal injection, sterile normal salt solution was brought to a boil and the powder slowly dropped in. Long has found that no further sterilization is necessary. The solution should be prepared just before using.

Comment. As with any new drug, the therapeutic value of this new chemotherapeutic agent can be determined only after prolonged use. In this one case, however, it appears that para-amino-benzene-sulfonamide produced a powerful bacteriostatic effect in a fulminating case of beta hemolytic streptococcic meningitis. Twenty-four hours after the injection of 1.6 gm. subcutaneously and 0.016 gm. intraspinally the spinal fluid cell count dropped from 5181 to 1026. Throughout the course there was a steady decrease in the cell count and on the tenth day following treatment the cell count had dropped to 78 and on the twenty-second day to 40.

The cerebrospinal fluid pressure before treatment was 440 mm. of water. Within 24 hours, the pressure dropped to 240 mm. of water, and thereafter did not exceed 200 mm. except on one occasion, when the patient was straining during the puncture, when it was found to be 300.

Before treatment, the spinal fluid cultures were found to be positive for beta hemolytic streptococci, both in the Frederick City Hospital and at the University Hospital. For two days following the institution of treatment, cultures of the organism grew out promptly within 24 hours. On the third day following treatment, the growth became sparse and required 36 hours. On the fourth day a few gram-positive cocci were found in the smear, but the culture was sterile. Following this, 10 consecutive negative cultures were obtained. This behavior of the spinal fluid cultures is further evidence of the bacteriostatic power of the drug on beta hemolytic streptococci. This marked reduction in cell count corroborates Schwentker's finding [3] that the drug itself produces no cellular response in the leptomeninges. Furthermore in this case, the inflammatory reaction of the leptomeninges was greatly decreased after one intraspinal injection.

Because of the existing peripheral facial paralysis at the time the patient was admitted to the hospital, it was felt that she had a mastoid infection and that the portal of entry was through the mastoid, even though there was no swelling in the region of the mastoid. Because of the heretofore hopeless outcome of streptococcic meningitis, it was thought best to see if the patient responded to the drug before subjecting her to a mastoidectomy. That the drainage of the mastoid bore no relation to the decrease in meningeal reaction is shown by the fact that the spinal fluid cultures became negative on December 23, twenty-four hours before the mastoidectomy was performed. This operation was considered worthwhile at this time only because of the striking improvement in the patient's general condition.

In the treatment of streptococcic meningitis with this drug, the exact required dosage is as yet undetermined. The dosage given this patient seemed to be adequate and until further data are forthcoming it is suggested that the intraspinal injection be continued until three consecutive negative cultures are obtained, and that the oral administration be continued for 10 days following the last positive spinal fluid culture. As pointed out by Long, unless the drug is given for a sufficient length of time there may be a relapse of the infection.

Whether or not parenteral and oral administration of the drug will control infection in the central nervous system without intraspinal injection has not yet been determined.

The drug is relatively non-toxic but two complications, sulphemoglobinemia and acidosis, are occasionally encountered. Should either occur, the drug should be discontinued or the dosage decreased for 24 to 48 hours. Acidosis may be relieved by parenteral injection of 5 per cent sodium lactate.

I wish to express my appreciation to Dr. Perrin H. Long and Dr. Francis F. Schwentker for supplying me with the drug and for their suggestions in the treatment, to Dr. Charles Bagley, Jr., for permission to publish the case, and to Dr. N. Davidson for his assistance in treating the patient.

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INTERMITTENT HYPERTHERMIA OF SEVEN YEARS' DURATION *

By EDGAR V. ALLEN, M.D., F.A.C.P., *Rochester, Minnesota*

A MECHANICAL engineer, 38 years old, was admitted to the Clinic September 27, 1935, complaining of attacks of fever during a period of seven years. The patient was born in Dayton, Ohio, and moved to southern California at the age of eight years. He had never been in the tropics, in South or Central America, or in Mexico other than in parts within 50 miles of the California border. He had had measles and whooping cough as a child, and while serving in the Navy in 1918 had had measles complicated by lobar pneumonia.

Between the ages of 23 and 35 he had had severe frontal headaches associated with photophobia, but without nausea and vomiting. In 1926 repeated washing of both antrums relieved the headaches markedly but not completely. In 1928, at the age of 31, he had an attack of influenza characterized by malaise, fever and weakness. There was no associated somnolence or insomnia. About six weeks later he experienced the first of the attacks of fever, which attacks had occurred intermittently ever since.

The attacks of fever varied greatly in intensity (figure 1). They were preceded by prodromal symptoms by as much as 24 to 48 hours, such symptoms consisting of aching in the neck, shoulders, small of the back and feet and ankles, and often in the hands and wrists. Chilliness, and often severe chills, were experienced. Occasionally nausea and vomiting occurred as the temperature of the body increased. When the temperature reached the maximum, the patient perspired profusely and his temperature then began to decrease. Usually he slept during the time his temperature was returning to normal. He would lose from four to seven pounds (1.8 to 3.2 kg.) during such attacks.

* Read before the meeting of the Minnesota Society of Internal Medicine, Duluth, Minnesota, June 6, 1936.

From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota.

Twenty-four hours after an attack the patient felt entirely well. In later years, severe chills and nausea which had formerly almost invariably accompanied episodes of fever had become very rare, and aching of the legs, which had occurred as a prodromal symptom in the earlier years, had been replaced by aching of the feet and ankles. Aching in the neck, shoulders and small of the back had occurred with the attacks only in the past three or four years. The attacks had gradually increased in

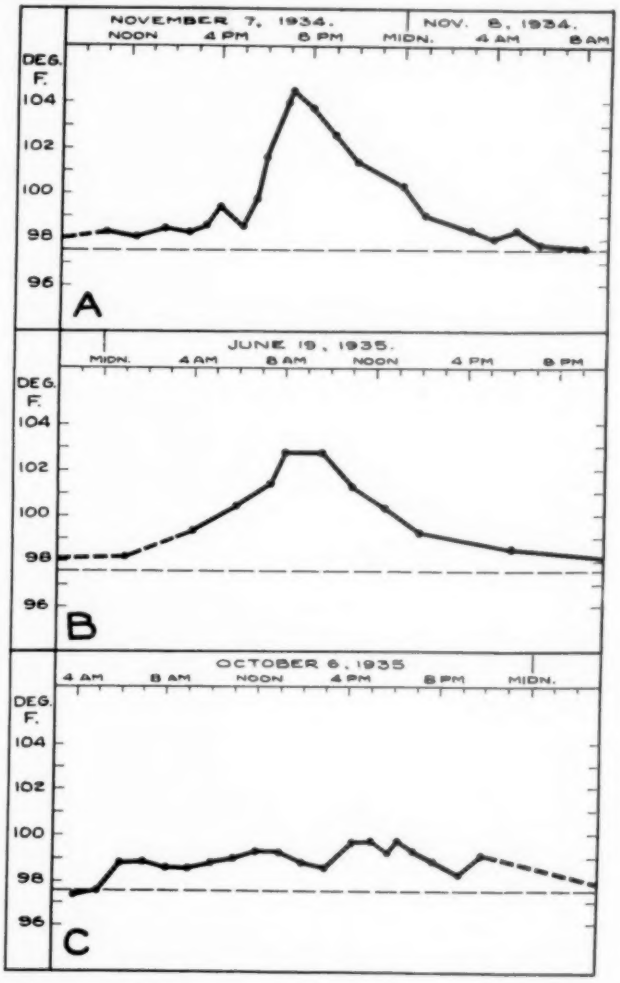

FIG. 1. The inconstancy of the response shown by charting the temperature of the body during three (*A*, *B* and *C*) spontaneous attacks of fever.

number from about 10 in 1929 to 46 in 1935. The average of numerous determinations of body temperature between episodes of fever was roughly 97.6° F. The longest interval in which no attack had occurred had been 100 days, in 1933. Complete records had been kept in 1934 and 1935, and during this time the longest interval between attacks was 15 days, and the shortest, six days. The mild and severe attacks occurred with no regularity, there being no relationship between the intensity of attacks and the interval between them (figure 2).

During the six years prior to examination at the Clinic the patient had been under the supervision of a number of physicians, but their examinations had always given essentially negative results. Agglutination tests for undulant fever, examination of the blood for malarial organisms and spirochetes, urinalyses, and various roentgenologic examinations, had always been negative. Neoarsphenamine (given

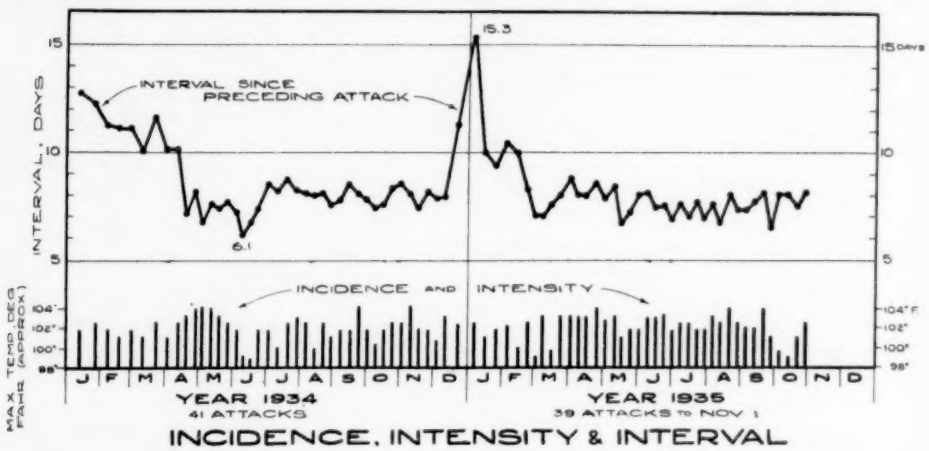

FIG. 2. The upper part of the chart indicates the intervals between attacks: during 1935 and 1936, the shortest interval between episodes of fever was six days, the longest 15 days. The temperatures attained during attacks, which varied from 98.8° to 104.4° F., are shown in the lower part of the chart.

intravenously four times at weekly intervals), oxyquinoline sulphate (given in retention enemas and by mouth for several months) and quinine sulphate (in amounts of 20 grains [1.3 gm.] during the prodromal stages of three attacks), had been without benefit. Two brands of acetylsalicylic acid (empirin and aspirin) have been found to lower the body temperature substantially, although the fever persisted over a longer period when these drugs were taken.

Physical examination at the Clinic revealed small tonsils and evidence of sinus infection. No evidence of any abnormality was found on examination of the heart, lungs, abdomen, lymph nodes, and extremities, or prostate gland, seminal vesicles, and epididymides. A complete neurologic examination also gave negative results. Proctoscopic examination showed nothing significant. Examination of the eyes was negative except for evidence of old choroiditis on the nasal side of the right macula and a small opacity near the periphery of the lower nasal quadrant of the right lens. The blood pressure in millimeters of mercury was 100 systolic and 70 diastolic. Routine examination of the urine and blood, including determination of the values for hemoglobin and blood urea, enumeration of erythrocytes, examination of blood smears, and a serologic test for syphilis, were all negative. Leukocytes numbered 8,300 per cubic millimeter of blood, of which 46 per cent were lymphocytes, 6 per cent monocytes, 46 per cent neutrophiles and 2 per cent eosinophiles. Bronchoscopic examination failed to reveal any evidence of bronchiectasis. Visualization of the kidneys following the intravenous injection of neo-iopax showed them to be entirely normal. Agglutination tests of the blood for *Pasturella tularensis* and *Brucella abortus* were negative. A tuberculin test was positive. Roentgenologic examination of the sinuses disclosed markedly thickened membrane in the right antrum, and that of the teeth some evidence of infection in one tooth. There was no growth of organisms on culture of the urine. Cultures from the nasopharynx revealed streptococci,

and those of prostatic secretion both streptococci and staphylococci. The sedimentation rate of erythrocytes was 5 mm. in one hour.

The patient was then observed in the hospital during an attack of fever. His temperature rose from 97.2° to 100.4° F. in eight and a half hours, and then decreased to 97.6° F. in three and a half hours. The pulse rate increased to 120 beats per minute. Urine, passed when the temperature was 101° F., was normal. Examination of blood smears for malarial organisms, spirochetes and trypanosomes was likewise negative at this time. Leukocytes numbered 20,000 per cubic millimeter, 28 per cent being lymphocytes, 3 per cent monocytes, 67 per cent neutrophiles, 1 per cent eosinophiles and 1 per cent basophiles; there was evidence of moderate toxicity of the leukocytes. The sedimentation rate was 7 mm. in one hour. Spinal puncture, made when the temperature was 101.0° F., showed normal pressure responses; analysis of the spinal fluid gave negative Wassermann, Kline and Nonne reactions and revealed 3 small lymphocytes per cubic millimeter, the total protein being 30 mg. and the colloidal gold curve 0 111 100 000. Blood cultures on brain broth and on blood agar were negative.

On October 2 the infected tooth was removed, cultures from the root revealing streptococci. Because washings from the right antrum were purulent and contained streptococci and because the left antrum appeared to be involved in a similar manner, bilateral antral windows were made on October 8, 1935. On November 27 and 28 roentgen treatment * was given to the right and left sides of the head respectively. On November 2, subcutaneous injections of a vaccine made from organisms cultured from the nasopharynx were begun, injections being given twice weekly for five weeks in increasing doses, and subsequently in constant doses every week. None of these procedures influenced the recurrence of attacks in any way.

The patient was observed during several spontaneous attacks of fever. Possibility of malingering was excluded by constant observation and by use of an automatic rectal thermometer. During an episode of spontaneous fever 1/6 grain (0.01 gm.) of pilocarpine was administered hypodermically; profuse salivation and sweating followed but the fever was not influenced in the ensuing hour. Three grains (0.20 gm.) of sodium amytal administered by mouth then induced sound sleep although the fever was unaffected (figure 3*A*). At another time phenobarbital given in sufficient amount to cause somnolence did not prevent or modify an attack. During a subsequent attack ergotamine tartrate was given subcutaneously in amounts of 0.25, 0.25, 0.25, 0.25 and 0.50 mg., respectively, at hourly intervals; the course of the fever was unchanged (figure 3*B*). The temperature response to intravenously injected typhoid vaccine (figure 3*C*) was about the same as that observed during spontaneous episodes of fever (figure 3*D*). The response of body temperature to increased environmental temperature in a Simpson-Kettering fever cabinet and in a full-length body baker was considered normal (figures 3*E* and *F*). During a spontaneous attack, when the oral temperature was 102.0° F., 1/4 grain (0.016 gm.) of morphine sulphate was given subcutaneously. The temperature increased another degree in the next hour, and remained at this height for two hours when spontaneous sweating set in and the temperature dropped (figure 3*G*). Although the patient slept during this period, no influence on the course of the fever was noted. In another attack amidopyrine was administered three times, in amounts of 10 grains (0.65 gm.) at hourly intervals. The first dose induced some sweating and momentarily suspended the rise of the fever; after the second dose moderate sweating continued and the fever dropped, but not until nine hours later did it reach the individual normal of 97.6° F. (figure 3*H*). During another spontaneous attack 15 grains (1.0 gm.) of "larodon" (Hoffman-La Roche, Inc.) was given by mouth when the oral temperature reached 100.0° F.; an equal amount was given an hour later. The temperature only slightly exceeded

* 135 kilovolts, 16 inches, 5 milliamperes, 6 mm. aluminum filter, 20 minutes.

100.0° F. and returned nearly to normal in seven hours; the fever recurred, however, eight hours later, and 15 grains of larodon was again given. Some effect on the temperature was again noted, but it did not become normal until 13 hours after the last (29 hours after the first) administration of larodon (figure 3*I*). These results

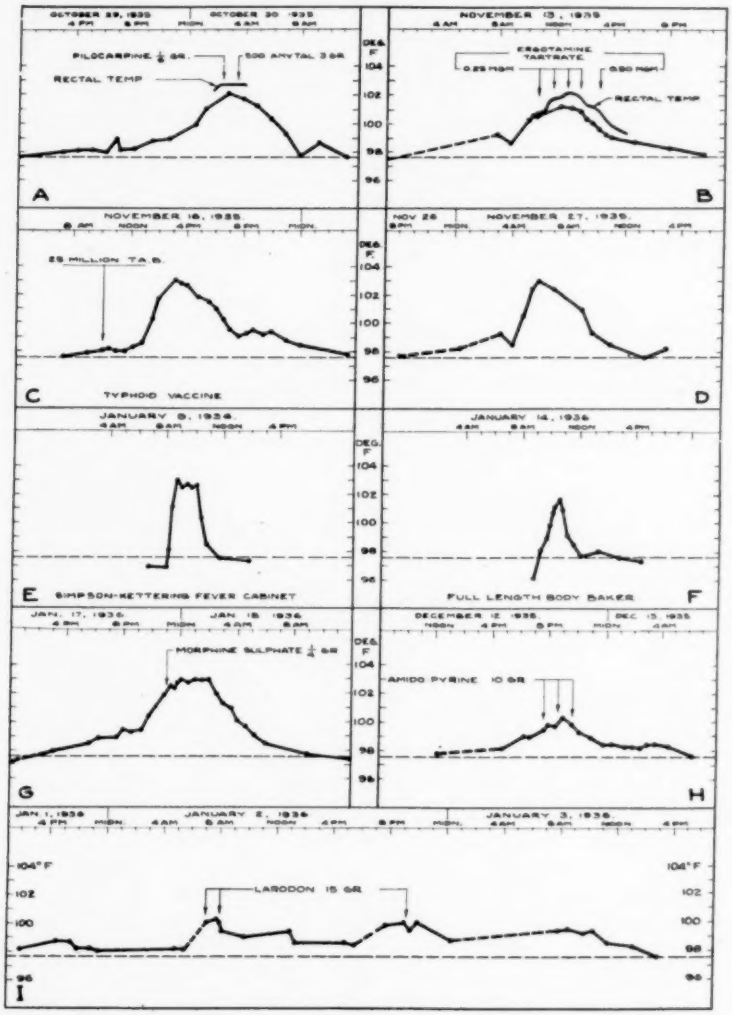

FIG. 3. *A*, *B* and *G* illustrating the absence of effect of pilocarpine, sodium amytal, ergotamine tartrate and morphine sulphate on the fever, *H* and *I*, the effects of amidopyrine and larodon in decreasing the fever, *C*, fever induced by injecting typhoid vaccine intravenously, which simulated closely that occurring spontaneously *D*, *E* and *F*, the response of the body temperature to increased environmental temperature, which was considered normal.

were similar to those sometimes noted by the patient on using acetylsalicylic acid (empirin and aspirin) prior to coming to the Clinic.

Typhoid vaccine was injected intravenously November 16, 18 and 30, and December 2 and 4 in amounts of 25, 40, 60, 85, and 120 millions of killed organisms,

respectively. On each occasion the oral temperature was elevated to between 102.7° and 103.3° F. The reactions, including symptoms and fever, were identical to those noted during spontaneous attacks of the same degree of fever. Spontaneous attacks of fever were experienced on November 27 and December 12. The first occurred on the ninth day after an injection of typhoid vaccine and on the fourteenth day after the preceding spontaneous attack; the second spontaneous attack occurred on the eighth day after an injection of typhoid vaccine and on the sixteenth day after the preceding spontaneous attack. Spontaneous attacks then occurred December 18 and 24, and on January 2, or at intervals of approximately six days. These results suggested that the fever induced by the intravenous injection of typhoid vaccine served as a substitute for the spontaneous attack, inasmuch as an interval of 14 or 15 days between spontaneous attacks had occurred only once in the last two years.

In the hope that fever induced artificially by any means would substitute for spontaneous attacks, on the sixth day after a spontaneous attack the body temperature was elevated to 103.0° F. by mouth (103.4° F. by rectum) and was kept at or near this level for an hour in a Simpson-Kettering fever cabinet. One day after this fever treatment, or seven days after the spontaneous attack, moderate spontaneous prodromes appeared and persisted for about two days, but no fever was observed. Five days after this fever treatment, or 12 days after the preceding spontaneous attack, the temperature was raised to 101.7° F. (by mouth) in an ordinary full-length baker and was kept there for a few minutes. A spontaneous attack occurred four days later, or 15 days after the preceding spontaneous attack and nine days after the fever artificially induced in the fever cabinet. This suggested that the higher temperature maintained for an hour in the fever cabinet served as a substitute for a spontaneous attack and showed definitely that the lower temperature attained in the body baker for a short period did not so substitute. It should be noted that the total "fever area" in the first instance was over twice as great as in the second.

During another attack of fever, three injections of 9 minims (0.5 c.c.) each, of epinephrine were given at hourly intervals without effect on the fever. Another episode of fever occurred while the patient was taking phenobarbital, which made him very drowsy; 1 c.c. of pituitrin injected subcutaneously and 20 c.c. of whole blood injected intramuscularly did not influence the fever.

On February 3, 1936, Dr. E. C. Rosenow began a study of the patient from a bacteriologic standpoint. Blood agar platings of material from the nasopharynx and of pus expressed from the tonsils revealed unusually large numbers of green-producing streptococci. The cataphoretic velocity of these streptococci was normal. Skin tests made with the euglobulin fraction of the blood serum of horses, injected for immunization purposes with neurotropic and arthrotropic types of organisms, revealed a marked reaction in each instance, apparently indicating antigen of these organisms in the skin. Administration to the patient of the serum of horses so treated, on three successive days, greatly diminished this skin reaction, indicating, apparently, almost complete neutralization of the antigen in the patient's skin, although an attack of fever occurred at the expected time.

At this time the leukocytes numbered 7,400 per cubic millimeter of blood, 84 per cent of them being neutrophiles, 7 per cent monocytes and 9 per cent lymphocytes. The sedimentation rate was 7 mm. in one hour. On February 9 serum sickness began; this was characterized by a temperature as high as 103° F., and by urticaria, chilly sensations, drowsiness and somnolence and generalized aching and erythema. The hands and feet were hot and swollen; the hands felt "asleep" at times, and there was slight aching of the eyes and head. The symptoms mentioned were moderately acute for three days and recovery was not complete for about a week after the symptoms began.

Tonsillectomy was performed February 13. Culture of the tonsils revealed the

same type of organism shown previously to be present in the nasopharynx and secretion from the tonsils. Two days after tonsillectomy another attack of moderate fever was experienced and, the following day, the fever was associated with acute bronchitis; this, however, disappeared rapidly.

The patient left our supervision on February 19, in order to return to his home, and his subsequent condition was reported by letter. He remained well. His physical and mental energy increased, he slept better, and in general his health was substantially improved over that of the preceding few years. Episodes of fever did not occur. In May, however, he wrote that intermittent nasal discharge, photophobia, and headache indicated sinus infection. His diagnosis seemed well founded, for on June 30 (136 days after the last episode and 137 days after tonsillectomy) a severe febrile episode occurred. This could hardly be a spontaneous remission since the longest interval between attacks in seven years had been 100 days and the longest interval in the preceding two years had been 15 days. After recovery from the attack just mentioned a physician confirmed the diagnosis of frontal sinusitis and non-surgical treatment was begun. Attacks of fever occurred at intervals of 68, 25, 14, 25 and 13 days.*

Comment

It was apparent from the history of this patient's illness that an etiologic basis for the recurrent attacks of fever would be difficult if not impossible to establish. This assumption was strengthened by the paucity of findings from examinations elsewhere and from routine examinations at the Clinic. The patient, however, was coöperative and was desirous of obtaining a cure for his condition, regardless of the length of time required or the inconveniences which such an intensive investigation would entail. The possibility that the patient was malingering was eliminated promptly by observing him during episodes of fever and by personally determining his oral and rectal temperature. The elevation of the pulse rate was further evidence that the fever was real.

The first diseases to be considered were malaria, bronchiectasis, pyelitis or pyelonephritis, bacilluria, Hodgkin's disease, undulant fever, filariasis, trypanosomiasis, spirochetosis, tularemia and the blood dyscrasias. No evidence of any of them was found. A transcription of the patient's record was subsequently sent to Colonel Charles F. Craig, Director of the Department of Tropical Medicine at Tulane University, in the faint hope that the patient might have some unusual tropical disease with which we were unfamiliar. Colonel Craig kindly reviewed the record and replied that he was quite certain that the condition was not one of tropical infection.

The next step was elimination of obvious foci of infection, although there was little hope that such a procedure would influence the attacks of fever. When the surgical treatment of infected antrums and extraction of an infected tooth were unavailing, it was apparent that the situation was a difficult one and that investigation along the lines reviewed and discussed by Dr. H. A. Reimann, of the University of Minnesota School of Medicine, should be carried out. The possibility of a psychogenic fever was promptly eliminated by failure of morphine and amytal to influence the fever reactions. Further, an attempt was made to influence the fever by roentgen irradiation of the head, after considering the possibility that the fever was of central origin and was caused by a disturbed heat-regulating center. No results were obtained by these measures and in desperation an attempt was then made to eliminate the spontaneous at-

* At this time (January 15, 1937) the patient is experiencing episodes of fever of about the same type as before tonsillectomy was performed.

tacks of fever by inducing it artificially. While the results of this procedure were valueless from a preventive standpoint, there was considerable but not conclusive evidence that artificially induced fever substituted for the spontaneous attacks. Finally, further consideration was given to the possibility that the fever was of infectious origin. Reimann has reviewed evidence that fever of infectious origin responds to antipyretic drugs, while normal temperatures and psychogenic fevers do not. Our studies indicated that the antipyretics, amidopyrine and "larodon," definitely influenced the fever, whereas pilocarpine, ergotamine tartrate, morphine, amytal and epinephrine did not. These results suggested that the fever was produced by infection. This was further suggested by an increase in the number of leukocytes per cubic millimeter of blood and an increase in the percentage of neutrophiles on one occasion, and by an increase in the percentage of neutrophiles without an increase in the number of leukocytes during fever on another. Dr. Reimann then reviewed our study records and reported that he believed the fever was quite definitely of infectious origin, probably from some focus of infection.

It is interesting that there was no significant increase in the sedimentation rate. However, Reimann has pointed out that failure of the speed of sedimentation to increase during fever does not exclude an infectious origin. Because of the possibility of some hidden focus of infection, Rosenow's hyperimmune streptococcus antiserum was given, but an attack of spontaneous fever occurred at the expected time. Serum sickness followed the administration of horse serum, and before a sufficient interval had elapsed to determine whether or not another episode of fever would follow, tonsillectomy was performed because the tonsils were the only remaining possible focus of infection. Much to our surprise attacks of fever did not occur subsequently while the patient was under our observation, and he has reported that none occurred for four and a half months after his dismissal from the Clinic. He reported further that his general health had improved greatly. The evidence is quite clear, therefore, that either serum sickness or tonsillectomy produced the good therapeutic results. The former assumption appears quite untenable, and there can be no reasonable doubt but that the organisms in the tonsils were responsible for the recurrent attacks of fever. A return of episodes of hyperthermia after the longest free interval in seven years was definitely associated with frontal sinusitis. It seems fairly certain, therefore, that the episodes of hyperthermia were of infectious origin and that the organisms responsible for them lodged in the tonsils and sinuses.

Summary

Study of a patient who had recurrent episodes of hyperthermia for seven years indicated that his fever was of infectious origin. Tonsillectomy produced temporary cessation of these attacks of fever when all other methods of treatment which were tried had been without avail. Recurrence of attacks was associated with frontal sinusitis.

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PRIMARY CARCINOMA OF THE LIVER WITH BONE METASTASIS *

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PROVED cases of primary carcinoma of the liver are few in number, particularly so in comparison with the frequent occurrence of secondary neoplasms of that organ, which are found in about 2.5 per cent of autopsies. Distant metastases of new-growths primary in the liver are potentially common because of the characteristic tendency of the cells to invade the walls and lumina of the venous radicals. Of these metastases, one of the most unusual is that to the skeletal system, a search of the literature revealing only the following nine instances.

Schmidt,[1] in a man of 55, found a primary tumor in the right lobe of a cirrhotic liver, which had invaded the portal veins, and metastasized to the retroperitoneal tissues, lungs, bronchial glands, skull, sternum and sacrum. Bile capillaries containing yellow staining pigment were noted among the neoplastic cells in the metastases.

Huguenin's [2] case occurred in a man of 50 years who was known to have had a nodular liver for five years before death. At autopsy, the liver was cirrhotic and contained numerous reddish and green tumors, the former type showing venous invasion microscopically. Metastases were noted in the clavicle, and the dorsal and lumbar vertebrae.

Blumberg [3] found a soft gray-green nodular tumor the size of a fist in the right lobe of the liver of a 64 year old man known to have had both lues and diabetes. Metastases to the first, second, and third dorsal vertebrae were present.

The case reported by Catsaras [4] occurred in a man 65 years of age. A neoplasm in a previously cirrhotic liver had invaded the portal veins into their finest ramifications. Metastases to the neck of the femur caused a pathologic fracture. Bile production in the metastatic tumor cells was noted.

Moon's [5] case, in a 45 year male negro, also had a pathologic fracture of the right femur. A cirrhotic liver was studded with soft green nodules. Venous invasion by tumor tissue, as well as bile in the metastases, were found microscopically. Other metastases were bilaterally peribronchial.

Geschickter and Copeland [6] record a case of primary liver neoplasm in a 70 year old male negro, with metastases to pelvis, femur and spine.

Prym [7] found neoplastic liver cells in a biopsy specimen from a calvarium mass. Bile production and fat infiltration were present. Though no autopsy was done, a large nodular liver was palpable through a relaxed abdominal wall.

Kaufmann [8] described a case in a man of 33 years who had a tumor in the right lobe of a non-cirrhotic liver, with metastases to pelvic bones, ribs, vertebral bodies, lungs, and abdominal lymph nodes.

Karajanopoulos [9] found in a man 54 years of age, a tumor in the right lobe of a previously cirrhotic liver, which had metastasized to the manubrium sterni, thoracic vertebrae, and abdominal lymph nodes.

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Case Report

A white woman, 29 years of age, was admitted to the orthopedic service of Dr. B. Koven, at the Beth-El Hospital, Jan. 25, 1933, complaining of pain in her left thigh of three months' duration, intermittent but gradually increasing in severity. Terrific pain had confined her to bed for four days before admission.

Her family and past personal histories were negative. No gastrointestinal or urinary symptoms were noted.

The essential findings on physical examination were a shortening of the left lower extremity, outward bowing in the upper third of the corresponding thigh, with crepitation and tenderness at that point. A soft mass the size of a tangerine, adherent to the underlying bony structure, was felt over the eleventh rib below the left scapular angle. No abdominal masses were palpable.

On examination of the blood the hemoglobin estimation was 80 per cent (Sahli), the red blood cells numbered 4,200,000, the white blood cells 7,400 per cu. mm. with 76 per cent polymorphonuclear neutrophiles. The urinary findings, including the examination for Bence-Jones protein, were negative. The blood Wassermann reaction was negative. Nothing unusual was found in the blood chemistry examinations.

Roentgenographic examination demonstrated a pathologic fracture through a neoplastic involvement in the upper third of the left femur, and a similar involvement of the left eleventh rib.

Biopsy of the thoracic mass was done, but the patient died suddenly before a microscopic examination could be made.

Necropsy was performed two hours after death. The body was noted as that of a well developed, fairly well nourished, white woman, about 120 lbs. in weight. The left lower extremity was one and a half inches shorter than the right, with abnormal mobility and crepitation at the junction of the upper and middle thirds. A recent 10 cm. incision, closed by interrupted cat-gut sutures, through which considerable fluid blood exuded, was present over the eleventh rib in the left scapular line. Nothing found in the head or neck was noteworthy.

Chest. The sternum, the right ribs and pleural cavity, and the heart were grossly normal. The left fifth rib 2 cm. lateral to the costo-chondral junction was softened in an irregularly circular area 3.2 cm. in diameter. The overlying external periosteum and muscular tissue were necrotic, so that slight pressure caused a grumous, dirty, gray-brown material to exude from the rib; the underlying periosteum and parietal pleura were not grossly involved, although expanded a few mm. into the pleural cavity. On section the lesion was composed of the grumous material, old blood clot, and a few fine bony spicules. The same rib in the mid-clavicular line presented a fusiform bulge over an area of 2.5 cm. caused by an expanding neoplasm in its marrow, similar to the one found in the eleventh rib. The cortex at this point was destroyed and the periosteum moderately thickened. In neither case were the adjacent ribs involved.

The left pleural cavity contained about 200 c.c. of fluid blood free in the cavity above and below the tumor mass which, displacing periosteum and parietal pleura ahead of it, extended into the pleural cavity from the eleventh rib posteriorly. A small amount of blood was present in several fibrous walled loculi between tumor and lung. Wherever these were separated, the overlying parietal pleura and the periosteum (indistinguishably combined) presented a small, elliptical, smooth edged opening 6 by 3 mm., and several smaller linear openings which led into the tissue composing the tumor mass.

There was a recent operative incision, 10 cm. in length, extending parallel to the left eleventh rib posteriorly. To a point 2.5 cm. from its vertebral origin, this rib was completely replaced by a fairly soft mass which encroached upon the adjacent ribs. The subcutaneous operative area contained scattered recent hemorrhages and a

layer of cat-gut sutures. Viewed from the pleural surface, the mass was about 7 cm. in diameter and projected into the left thorax a distance of 5 cm., displacing thickened parietal pleura before it. There were recent diffuse subpleural hemorrhages over a radius of 10 cm. about the tumor. The mass on section was fairly soft, pale green in color, divided into large ovoid lobules by thin fibrous strands. The mass presented several necrotic and occasional faintly outlined hemorrhagic areas.

The eleventh rib was absent in this area, a suggestion of previous periosteum remaining near the still recognizable portion of the rib. The latter had a remarkably thinned cortex, 1 mm. in width at the tumor edge, the periosteum raised from its surface by tumor tissue and hemorrhage, and thickened to 1.5 mm. The marrow was soft and brownish and lacked trabecular structure.

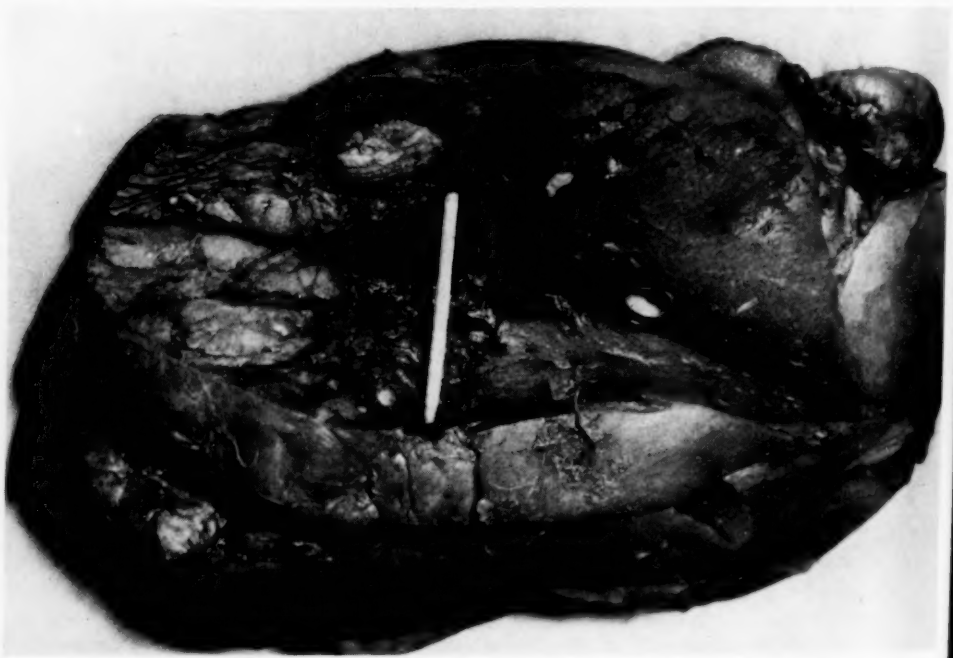

FIG. 1. Gross photograph of the liver showing the lobulated tumor occupying the greater part of the right lobe. Note the adjacent daughter nodules, the relatively sharp demarcation of tumor from neighboring normal parenchyma, and the absence of cirrhosis in either lobe.

In the three bones in which the marrow and cortex had been invaded by new growth with subsequent pathologic fracture, there was no gross evidence of attempted periosteal or endosteal new bone formation. The periosteum seemed to have been destroyed practically in situ and lifted only to a small degree by the expanding lesion. The adjacent, grossly uninvolved, marrow cavities were neither congested nor softened. After extensive sectioning, the lungs and thoracic lymphatic tissues presented no gross neoplastic involvement.

Abdomen. No free fluid or adhesions were present in the peritoneal cavity.

The *liver* measured 24 by 18 by 9 cm. and weighed 1400 gm. The outer half of the right lobe was almost completely replaced by a greenish yellow mass, 8.5 cm. in diameter, divided by fibrous septa into lobules of an average size of 1.0 to 1.5 cm. (figure 1). There were necrotic areas and irregular hemorrhages within these

lobules. Adjacent to the larger mass were several similar smaller nodules surrounded by a dark green hepatic parenchyma which was greatly compressed and contained discrete, ovoid, lighter green areas 2 mm. in diameter. This whole green area was sharply demarcated from the medial half of the right lobe by a narrow fibrous band which puckered the diaphragmatic surface.

The remaining hepatic parenchyma was well lobulated and showed no gross changes. No cirrhosis was present. The portion of Glisson's capsule overlying the tumor was thickened, shreddy, and adherent to the diaphragm. The gall-bladder had a thin wall; its mucosa was green, smooth and velvety. The biliary ducts were patent throughout and showed no gross alterations of any of their walls. The portal and pericholangitic lymph nodes, as well as the retroperitoneal subhepatic tissues were grossly uninvolved. The vena cava and portal veins and their larger branches showed no mural or luminal alterations.

The *adrenals, kidneys, genitalia* and *pancreas* showed no gross changes.

The *gastrointestinal tract* except for mucosal pallor appeared normal. There was no enlargement, induration or other change of the mesenteric lymph nodes. The thoracic duct and the portal and splanchnic vessels, the vena cava and its tributaries, the aorta and its branches were all grossly normal, including the pelvic vessels and the femoral vessels on both sides to the knee.

The *spine* showed no gross changes in the thoracic, lumbar and sacral portions.

Extremities. There was moderate edema of the left upper anterior thigh. The marrow of the left femur from a point 1.5 cm. below the midpoint of the junction of the neck and body downward for a distance of 10 cm. was completely replaced by rather soft, pale green neoplastic tissue (figure 2). None of the normal trabecular markings remained, the tumor tissue at the edge of recognizable marrow extending into the surrounding soft tissues. There was a soft, round, discrete, gray white nodule, 1.2 cm. in diameter, 1.8 cm. below the upper margin of the greater trochanter and 0.2 cm. from its posterior wall. The cortex was eroded from within and narrowed, tapering toward the line of a pathologic fracture which extended from a point 7 cm. below the upper margin of the greater trochanter downward, forward, and inward, for a distance of 2 cm. The tumor tissue here was friable and necrotic, apparently the seat of recent blood extravasation. The periosteum was torn through opposite the fracture, and raised by tumor tissue 1.5 cm. from the bone on either side. There was much hemorrhage into the muscles about the fracture. Evidence of healing was absent.

The breasts. Apart from the occurrence of a small intracanalicular fibroma in the right breast, both breasts were normal.

Microscopic Examination. Liver. Throughout the left lobe, and in the right lobe at more than a few centimeters from the mass described above, there are no evident histologic alterations. Nearer the mass, the sinusoids become congested so that in a zone of a few millimeters breadth around the mass the picture is one of extreme passive congestion, with red cells present between Kupffer and cord cells, and with the cord cells flattened, frequently separated and showing necrobiotic changes, from granular and vacuolar degeneration to total cyto- and nucleo-rhexis. There is in this zone marked distention of bile-capillaries with green granular pigment which gives a positive Gmelin test, and occasionally a positive Turnbull stain. In places this pigment outlines the bile capillaries, into the finer intercellular ramifications. A few sublobular and larger branches of the hepatic and portal veins are totally filled with tumor thrombi. This is observed in the sections taken within 2 cm. from the tumor edge, but is not present in sections further removed (figure 3). These thrombi most commonly show either total or partial neoplastic cellular necrobiotic changes; in several places they are permeated by fibrin, the tumor cells totally necrotic in the organized and recanalized mass. In one section in which all the venous branches are so occluded, two large branches of the hepatic artery are filled with fibrinplatelet

FIG. 2. Gross photograph of upper half of left femur showing pathological fracture (A), elevated periosteum and subperiosteal tumor (B), and a solitary nodule in the femoral neck (C).

thrombus, the surrounding hepatic tissue being completely necrotic and heavily infiltrated with partially hemolyzed red cells. The periphery of this sharply outlined area is surrounded by markedly congested normal liver tissue in whose sinusoids are huge numbers of leukocytes. There is no cirrhosis, bile stasis, or cellular infiltration in sections through grossly normal liver except as already noted. Glycogen granules and fat vacuoles (neutral fat) are present regularly and in apparently normal amount in all sections.

The tumor tissue is almost everywhere separated from the surrounding normal tissue by a layer of fibrous tissue, sparsely cellular and poorly vascularized (capillaries); nowhere can any patent transition from the surrounding normal tissue, nor any penetration through the delimiting fibrous tissue be seen, although in places the latter is thinned out almost to single strand thickness. Here and there just beyond the edge of the large mass are small, well circumscribed, round or elongated

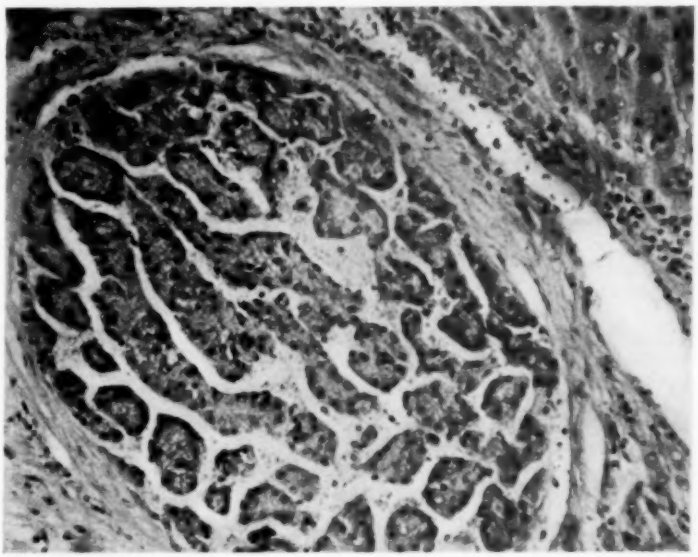

FIG. 3. Low power microphotograph of tumor thrombus occluding a sublobular hepatic vein. Note the neighboring inflammatory cellular reaction.

masses of similar cells surrounded by fibrous tissue, lying amid the normal hepatic tissue. In all places, however, where such masses do not totally fill such areas in medullary fashion, the delimiting fibrous tissue is seen centrally to be lined by a single layer of flattened endothelial cells, present throughout the periphery except at points where the cell masses extend into the wall. Erythrocytes are present between the cell masses in such incompletely filled areas. In a few places in the large branches of the hepatic vein around the capsule-like delimiting zone, about the large tumor as well as in some large sinus-like spaces within it, are isolated tumor cells, well preserved and stained, free within the lumen and not enmeshed by fibrin, red or wandering cells. Where larger masses are seen, necrobiotic changes and partial lumen occlusion, to a greater or lesser extent, are the rule.

The tumor itself, as well as the smaller daughter nodules, is composed of masses of cells, arranged chiefly in anastomosing strands two cells in thickness (figure 4). There is a marked tendency to radial arrangement of these strands, particularly in the central portion of the large mass, where an occasional vessel is present in the center

of such a radially arranged zone; these vessels, extremely few in number, are arterial in character. There is nowhere any suggestion of true lobular structure, although dense strands of fibrous tissue carrying capillaries and occasional arterioles penetrate the tumor for varying distances from the delimiting fibrous tissue, with which they are connected.

Between the cells of the individual strands one sees very frequently canaliculi partially or completely filled with finely granular pigment varying from a definite green-yellow to a dirty brownish yellow, giving the Gmelin stain regularly but only very occasionally the Turnbull stain. These capillaries are frequently markedly distended, particularly where the cell masses, cut in cross-section, appear as solid alveoli, and they can be traced as fine ramifications between the individual cord cells. Nowhere can any communication with larger ducts be seen; neither portal canal nor bile duct, nor any pigment phagocytosis is apparent in any section. The cord strands

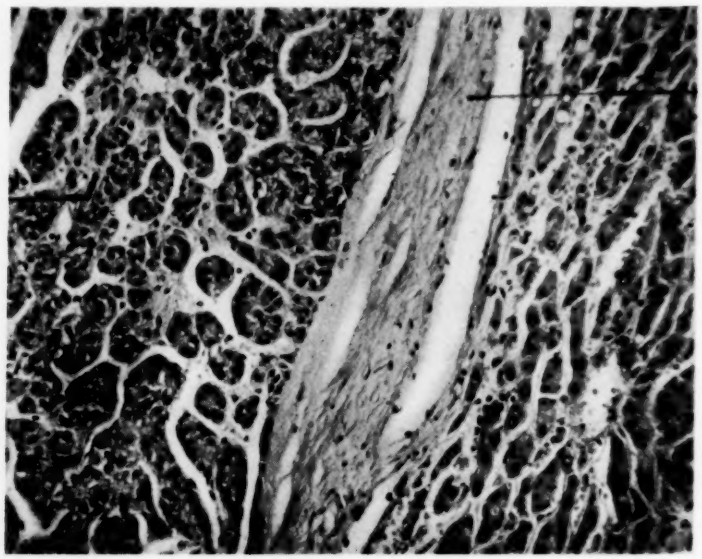

FIG. 4. Low power microphotograph of primary hepatic tumor (A) separated from normal liver by poorly vascularized acellular fibrous tissue (B).

are everywhere lined by flattened, stellate-shaped cells resembling in outline and nuclear characteristics Kupffer cells, but being more numerous and having somewhat larger nuclei than is usual in normal cells. In the irregular sinusoidal system between the cords are varying numbers of erythrocytes and scattered leukocytes.

The individual tumor cells are larger than the hepatic cord cells, measuring between 15 to 20 μ. They are well outlined and cuboidal in shape. They have considerable amounts of deeply staining homogeneous acidophilic cytoplasm, and a single round, large, vesicular but hyperchromatic, well-outlined nucleus, with the chromatin peripherally arranged but without well defined nucleolus. Mitoses are extraordinarily rare; there are no amitotic forms, nor do fusion forms or giant cells appear. The cells are remarkably uniform in appearance, except in the smaller intravascular daughter nodules where they are somewhat smaller. Bile canaliculi are absent in such nodules. There is remarkable absence of fatty vacuoles and glycogen granules both in the original growth and its metastases.

The *femur* shows the bone marrow to be replaced entirely by masses of neoplastic

tissue similar to that found in the liver and showing all the elements there described, including bile canaliculi and cord lining cells resembling Kupffer cells (figure 5). The cells are of the smaller variety, in medullary arrangement with small central necrotic areas (figure 6). Only here and there can distinct remnants of marrow

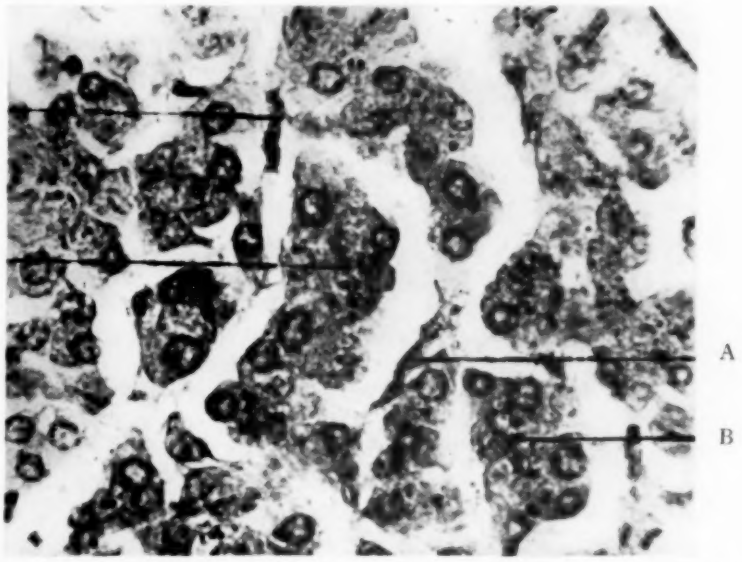

FIG. 5. High power microphotograph of femoral metastasis. Note the strand-like two-cell layered arrangement of the neoplastic cells and the elongated Kupffer-like cells (A) separating the cell cords from sinuses. At (B) are two bile capillaries.

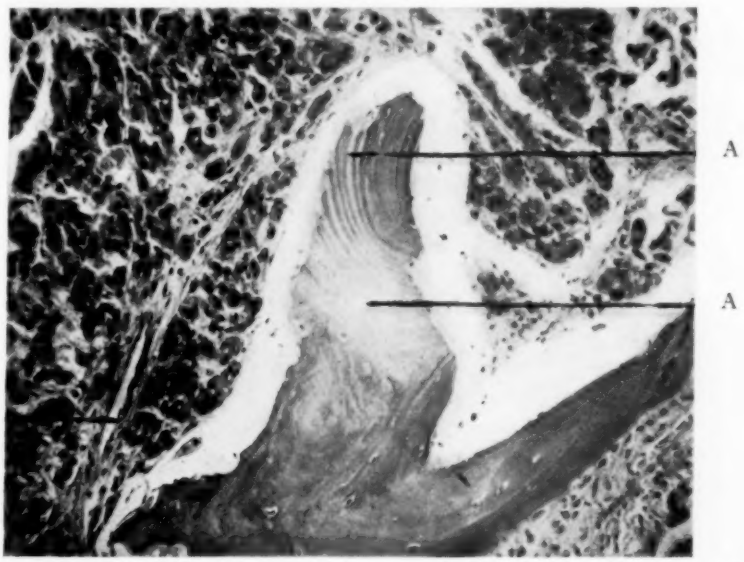

FIG. 6. Low power microphotograph of femoral metastasis. Note atrophic bone spicule showing decalcified area (A) and lamellae. At (B) is a small vessel resembling a sublobular vein.

reticulum fibers and small patches of erythrocytes, chiefly nucleated, be seen amid the tumor masses. As the line of fracture is approached, the cortical bone trabeculae are narrowed and on their marrow surface show erosions of various sizes, without any apparent osteoclastic hyperplasia, but with a marked and increasing deficiency in lime salts, so that in sections through the fracture itself the trabeculae are totally devoid of such salts, and are separated, with the tumor tissue extending through the line of separation to appear within the periosteum. Likewise toward the fracture from either side, but to a lesser extent than the lime absorptive process, the periosteum is widened, edematous, and very cellular, and the cells fibroblastic in type; at the fracture line, there is a distinct tendency for the cells to be arranged at right angles to the long axis of the bone.

Periosteum and endosteum, indistinguishable in the fracture zone, are infiltrated with moderate numbers of polymorphonuclear leukocytes; elsewhere the lymphocytes predominate in the periosteal infiltrate, while the endosteum is devoid of infiltration. Both the nutrient artery and arterioles in Haversian canals contain tumor cells, but nowhere are there completely plugged vessels.

Sections from areas in the femur not grossly involved, if taken from not more than 3 cm. beyond tumor edge, show an occasional tumor nodule or a few cells in vessel and marrow. Active erythropoiesis is apparent.

The ribs show, in all detail, histologic pictures corresponding to those described in the femur. No definite nutrient arterial embolization is demonstrable. Numerous sections of the lungs fail to disclose any tumor tissue within the vessels of whatever order.

This tumor is a primary parenchymal hepatoma, similar in gross appearance to several of those previously reported, though it did not occur in a previously cirrhotic liver. It is the only case with bone metastases reported in a woman, and occurred at 29 years of age, while seven of the nine others were found in patients over 45 years of age. Characteristic extensive vascular invasion and bile production in the metastases were present. As in six of the reported nine cases, evidence of metastases in the lung bed were not found after extensive search. This suggests a specific affinity of the neoplastic cells for the bone marrow in these cases.

The origin of this type of neoplasm is probably in the benign adenoma, whether this be of the congenital type not uncommonly found at the autopsy table or of the type due to proliferation in a parenchyma distorted by cirrhotic changes. That the neoplasm is usually single rather than multicentric in origin is suggested by the frequency with which only a right lobe neoplasm is found (five of the eight cases reported in detail, including our own).

The tumor acts like an organ rather than tissue in its metastases; these present all the structures of the normal liver, including cords of cells in double rows, intervening capillaries, and Kupffer cells. Bile and bile canaliculi are found, the former not undergoing phagocytosis by the Kupffer cells. That the metastasis may have the physiologic activity of the original organ is suggested by the bile formation present in our case. That such functions are not, however, completely the counterpart of the original organ, either in the primary neoplastic focus or the metastases, is suggested by the absence of glycogen granules and fat within the tumors, while the normal liver contained both.

From the standpoint of the clinician, attention should be directed toward the liver in those cases coming under observation with metastatic lesions, espe-

cially those of spine and femur, typically expanding in character and lacking new bone formation, in which the usual primary sites, lung, prostate, thyroid, breast and kidney have been excluded. The liver is likely to escape serious attention because of the tendency of a primary hepatoma to involve one lobe, thereby not interfering with liver function tests, rarely producing jaundice or ascites, and not usually causing appreciable hepatic enlargement or nodulation. Thorotrast injection may aid in outlining such tumors which are most frequently few in number, fairly well demarcated, and sufficiently large to yield shadows if outlined.

Summary

A case of primary liver carcinoma (hepatoma) with bone metastases is reported. Nine cases from the literature are collected and described briefly. Evidence is presented to indicate that this type of neoplasm is organoid rather than histioid, and shows in its metastases morphologic evidence of its original physiologic function. Attention is called to the liver as a focus for metastatic bone neoplasm in obscure cases.

The authors desire to express their thanks to Dr. B. Koven, attending orthopedist at the Beth-El Hospital, for permission to use the clinical data of this case, and to Dr. Thomas A. Gonzales, acting Chief Medical Examiner of the City of New York, for permission to use the pathologic data of this autopsy performed, as assistant medical examiner, by one of us (M. J.).

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ELECTROCARDIOGRAPHIC CHANGES WITH PERFORATED DUODENAL ULCER; A CASE REPORT*

By LEMUEL C. MCGEE, PH.D., M.D., HAROLD A. CONRAD, M.D., and ANGUS K. WILSON, M.D., *Elkins, West Virginia*

C. M., male, coal-miner, aged 39 years, entered the hospital one Sunday morning in shock and semi-coma. The history, obtained from his family, was that he had been seized with severe upper-abdominal pain while walking from one room to another in his home 12 hours previously, and that he had collapsed immediately. There had been no radiation of the pain to the sternum. He had become quite short of breath following the onset of pain and could not sleep. The pain had diminished but did not disappear. The next morning, 10 hours after onset of symptoms, a physician was called and the patient received a hypodermic, presumably of morphine. Some time afterward he started on a 50 mile trip, by ambulance, to the hospital.

Just at the time of his arrival, the patient had a recurrence of the excruciating pain in the epigastrium. He exhibited extreme dyspnea, dehydration, cyanosis and a truly rigid abdomen. After saline and glucose had been administered intravenously, the abdomen became pliable and the patient recovered somewhat from shock. An electrocardiogram (figure 1) was taken which presented inversion of T-waves in Leads II and III with elevation of the S–T interval in those leads as well as in Lead IV.

The sudden onset of pain in the epigastrium and the finding of marked rigidity of the muscles of the upper abdomen pointed to acute intra-abdominal disease with peritoneal irritation. The abdominal wall was not rigid for the subsequent few hours and during this time the patient vomited. A tentative diagnosis of either perforated duodenal ulcer or acute pancreatitis was made. When the cardiogram was developed, there arose the possibility of coronary occlusion with posterior surface infarction. The white blood count was 9,900 cells per cu. mm. The cervical veins were markedly distended and for a period of two hours there was definite pulmonary edema and a frothy sialorrhea. Heart sounds were faint, with a rate of 140 per minute. The red cell count was 4,740,000 and the blood Kahn was negative. Because of the lapse of more than 12 hours since the onset of the catastrophe and the persisting shock of the patient, the chance offered by surgery was described to the family as being very small. The family wished to have no surgery attempted and this was agreed to by the consulting surgeons and physician.

The patient was removed to a room in the hospital where, unfortunately, electrical interference makes the recording of the electrocardiogram very unsatisfactory, and hence no effort was made to repeat the tracing. A few hours later a third paroxysm of epigastric pain developed and, with it, the upper abdomen again became exceedingly rigid for a few hours. The pain at this time extended down in to the left flank. The vomiting continued.

In the periods between throes of severe pain with collapse, the blood pressure rose to 130 systolic and 80 diastolic from a brachial pressure too low to be read immediately after admission. The patient's temperature was, for the most part, between 99° and 100° F. rising but once to 100.6° F.

The patient recalled that for the previous six months he had had recurring attacks of rather severe epigastric pain with shortness of breath, and voluntarily stated that his abdominal muscles would become quite "hard" during the attack. The periods of distress were too numerous to count and they appeared only when he was working in the mines or when walking to or from his home. He was positive in

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the assertion that the discomfort was related to exertion, that the pain never extended into the chest or shoulders and that resting a few minutes provided relief. He had never observed that taking of food relieved him but had noticed that the pain was more apt to appear one to three hours after eating than at any other time. There had been no nocturnal distress but he had slept, by preference, on two pillows. For the previous four weeks he had had a cough and had noted faintness and giddiness. He had lost 10 pounds in weight. He drank five or six cups of coffee daily and had had to void urine twice each night. He had stopped work two weeks before because of

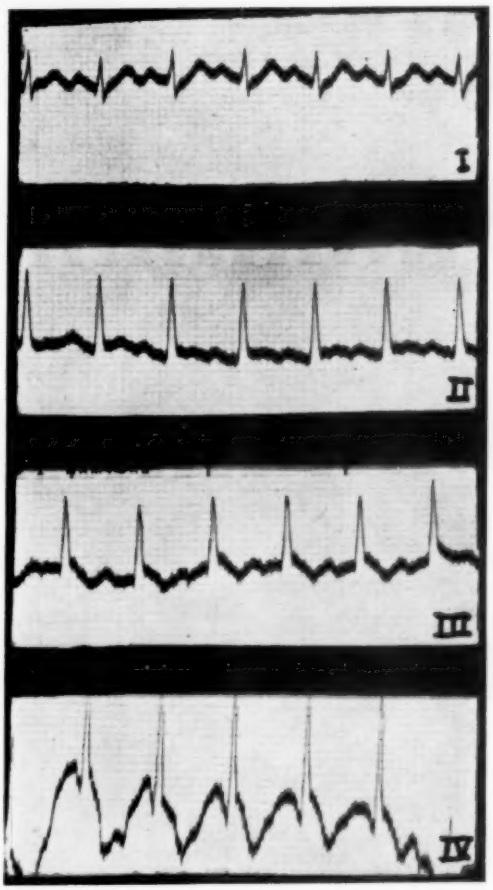

FIG. 1. Electrocardiogram taken at time of admission. Note low T_1, inverted T_3 and elevated S–T interval in Leads II and III.

marked dyspnea and weakness. He had been on no medication. In the past he had had a gonorrheal urethritis, a crushed foot, a broken nose, and a broken left arm. He had lost two wives from what had been diagnosed as pulmonary tuberculosis. His father, at the age of 75 years, had died after a chronic "gastric" complaint of several years' standing.

The abdomen became quite distended the day following the patient's admission. He received supportive treatment. He died after 70 hours in the hospital. The intriguing history, pointing to myocardial disease, and the terminal illness with death

from evident peritonitis, prompted an autopsy to ascertain whether there were two disease processes present.

The body was that of a man of about 170 pounds, appearing to be older than 39 years. Three liters of a greenish brown fluid were removed from the peritoneal cavity. The peritoneum was generally acutely inflamed. The omentum and superficial coils of bowel were matted with an abundant purulent exudate and thick fibrin. The duodenum was surrounded by both fibrin and firm fibrous adhesions extending to every adjacent structure. The fundus of the gall-bladder covered a perforation in the duodenal wall. The gall-bladder itself was intact but covered with exudate and fibrin. When the duodenum was opened, two typical, chronic "kissing" ulcers were found, the upper one alone having perforated. This ulcer measured about 5 mm. by 6 mm. in diameter and had thickened margins (figure 2).

The thoracic cavity contained no significant abnormalities. The pericardial sac was normal. The heart weighed 360 grams and the left ventricular wall was 15 mm. thick midway between base and apex but otherwise all measurements were well within normal limits. The coronary vessels were healthy in appearance except for a small atheroma in the left coronary about 2 cm. from the orifice. Careful dissection of these vessels revealed no occlusion. Extensive sectioning of the myocardium revealed no infarction, either old or recent. There were no other noteworthy findings at the autopsy. The histological study confirmed the interpretation of the gross pathological findings.

An occasional striking association between disease of the gall-bladder and symptoms referable to the heart has been noted in the past 30 years.[1, 2] Carmichael [3] noted a bradycardia in a patient having an obstructed cystic duct. The periods of bradycardia were observed three separate times, coinciding with strong contraction of the gall-bladder muscle. Tennant and Zimmerman,[4] in a statistical study of 1,600 autopsies, found "a significant association between the occurrence of heart disease in general and gall-bladder disease." Fitz-Hugh and Wolferth [5] reported six patients with cardiac complaints and abnormal electrocardiographic tracings who had gall-stones removed. A few weeks after the operation, the electrocardiographic abnormalities became normal in each patient. Willius and Fitzpatrick [6] found, in a series of 596 patients, a striking improvement in the cardiovascular condition after treatment for chronic disease of the gall-bladder, even in the group (229 patients) having organic disease of the cardiovascular system. The association between peptic ulcer and cardiac symptoms is undoubtedly less frequently noted. Barker, Wilson and Coller [7] reported, in 1934, an instance of perforated duodenal ulcer simulating the clinical picture of acute coronary occlusion.

The patient in the present report presented cardiac symptoms prior to the terminal illness. There was no evidence of chronic gall-bladder disease. It is obvious from the history and the finding of scar tissue about the duodenum that the patient had previously had "formes frustes" perforations of one or both the chronic ulcers. In the terminal catastrophe, the fundus of the gall-bladder had been employed to plug the perforation after three distinct leaks of the duodenum with a collapse accompanying each fresh emptying of duodenal contents. The electrocardiographic changes noted may have resulted from, (1) shock and low systemic blood pressure with insufficient oxygenation of the cardiac musculature, (2) embarrassment of circulation due to displacement of the heart by the elevated diaphragm, or (3) a reflex change in cardiac circulation and function initiated by the inflammatory process about the duodenum and gall-bladder.

A common experiment made upon frogs in the physiology laboratory is the production of a bradycardia or even cardiac standstill by light taps on the abdomen. This effect is lost when the vagus nerves are severed. There exists

FIG. 2. Photograph showing "kissing" duodenal ulcers. The ulcer on the left had perforated.

ample clinical evidence of the change in cardiac behavior in man initiated by reflexes arising from diseased abdominal viscera. However, it seems to the authors that the physiological changes accompanying shock in this patient were

likely of more import to the heart than reflexes from the acutely inflamed abdominal viscera. Because of the over-emphasis often placed by physicians upon the changes of the electrocardiogram in clinical practice, the findings in this patient are noteworthy. He had no serious heart disease that could be demonstrated after careful anatomic dissection.

Because of the occasional transient, non-specific R–S interval and T-wave changes in a variety of conditions, it is to be regretted that serial tracings were not available.

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EDITORIAL

THE AWARD OF THE JOHN PHILLIPS MEMORIAL MEDAL

THE John Phillips Memorial Medal has been awarded for 1937 to Dr. Richard E. Shope, of the Rockefeller Institute for Medical Research, at Princeton, New Jersey. The award is based on Dr. Shope's researches with filterable viruses which are regarded as outstanding in medical biology. Among these are: (1) the discovery of a tumor of rabbits, which now bears his name, and the demonstration that this tumor, which has many of the characteristics of a malignant neoplasm, is due to a filterable virus; (2) his contributions to the etiology and epidemiology of mad itch in cattle and the establishment of the identity of the virus causing this condition in cattle and that causing pseudorabies in swine; (3) the demonstration that swine influenza is not due to a single agent but is caused by an infection with a filterable virus and a hemophilic bacillus; (4) the production of evidence to focus attention on the possibility that the swine virus has at some time in the past been the agent in human influenza.

THE CHEMOTHERAPY OF HEMOLYTIC STREPTOCOCCUS INFECTIONS

THE report by J. G. Arnold, Jr., in this number of the ANNALS, of a case of grave hemolytic streptococcus infection which recovered under treatment with prontylin brings to the attention of our readers a new and promising chemotherapeutic agent.

The report by Domagk[1] in 1935 that the dye "prontosil" exerts a definite protective action in the case of mice infected with virulent hemolytic streptococci aroused widespread interest and stimulated many other workers to investigate the action of this substance. Domagk's findings have been confirmed and extended, particularly by Levaditi and Vaismen,[2] Colebrook and Kenny,[3] Buttle, Gray and Stephenson,[4] and Long and Bliss.[5] This preparation is of special interest since, with the exception of optochin in pneumococcus infections, it is the only instance of a drug which exerts a specific action on a bacterial infection.

[1] DOMAGK, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infectionen, Deutsche med. Wchnschr., 1935, lxi, 250.

[2] LEVADITI, C., and VAISMEN, A.: Action curative et préventive due chlorhydrate de 4'-sulfamido-2, 4 diamino-azobenzène dans l'infection streptococcique expérimentale, Compt. rend. Acad. d. sc., 1935, cc, 1694.

[3] COLEBROOK, L., and KENNY, M.: Treatment of human puerperal infections, and of experimental infection in mice, with prontosil, Lancet, 1936, i, 1297.

[4] BUTTLE, G. A. H., GRAY, W. H., and STEPHENSON, D.: Protection of mice against streptococcal and other infections by p-Aminobenzene-sulfonamide and related substances, Lancet, 1936, i, 1286.

[5] LONG, P. H., and BLISS, E. A.: Para-amino-benzene-sulphonamide and its derivatives, Jr. Am. Med. Assoc., 1937, cviii, 32.

Prontosil is the hydrochloride of 4-sulfamido 2, 4 diamino-azo-benzene. It is poorly soluble. " Prontosil soluble " is a related substance with a more complicated structural formula which is more soluble and is suitable for parenteral injection. Under the influence of reducing agents these compounds are decomposed in vitro into para-amino-benzene-sulphonamide (" prontylin ") which is believed to be the active ingredient of these substances. It is thought that a similar reduction is brought about in the body of animals treated with prontosil by the action of the streptococci themselves.

These workers in general agree that after intraperitoneal inoculation with highly virulent strains of beta-hemolytic streptococci, mice suitably treated with any of these substances recover or materially outlive the untreated control animals. Thus in experiments reported by Long and Bliss, untreated control animals receiving from 10 to 100 M.L.D. of culture invariably died on the first or second day, whereas the six treated animals in one series survived from six to 31 days, and in another series all six recovered. These results were obtained even though treatment was begun eight hours after infection and the mice gave positive blood cultures with 100 to 1000 or more colonies per c.c. of blood. Treatment had to be continued for some time or relapse and death occurred. Some difference was noted in the susceptibility of various strains of streptococci to the action of the drug. The results were much less definite when strains of low virulence were used.

The mode of action of the drug is not definitely known. Prontylin (but not prontosil) exerts a moderate bacteriostatic activity when added to cultures of beta-hemolytic streptococci, even in the presence of serum. The serum of animals treated with prontylin also shows an inhibitory effect on the growth of streptococci. No definite bactericidal effect, however, has been noted. Long and Bliss found that in their treated mice films from the peritoneal exudate made 24 to 72 hours after infection showed that active phagocytosis of the streptococci was taking place. At the same time the number of viable organisms in a drop of peritoneal exudate progressively diminished. In untreated mice this was not observed. They believe that the drug injures or affects the organisms in such a way that they become susceptible to phagocytosis. They could not confirm the observations of Levaditi and Vaismen that the drug inhibited the formation of capsules by the organisms. The drug showed relatively little or no protective power against the other species of organisms tested.

Favorable results have also been reported particularly in German and French journals from the use of these drugs in the treatment of human infections. In general these clinical studies were not carefully controlled and are less convincing than the animal experiments. Colebrook and Kenny treated 38 cases of puerperal infection with hemolytic streptococci and reported a mortality of 8 per cent as compared with an average mortality of 22 per cent in cases treated by other methods during the preceding four

years. Several patients who recovered had had a severe type of infection in which the prognosis would have been grave. Long and Bliss reported favorable results in a series of 19 cases of beta-hemolytic streptococcus infection of various types, including several cases of erysipelas and scarlet fever. One patient with otitis media and mastoiditis who recovered had shown a positive blood culture with over 2000 colonies per c.c. of blood. There were two deaths, one nine hours and one 22 hours after treatment was started. Both groups of workers were conservative in their claims as to the efficacy of the treatment.

Thus far relatively few untoward effects have been reported. A transient febrile reaction may follow the parenteral injection of large doses of the drug. It is readily absorbed both from the tissues and from the gastrointestinal tract. It is excreted quite promptly in the urine, and in cases with impaired renal function the possibility of a dangerous accumulation in the body fluids must be kept in mind. Signs of mild renal irritation have been noted in a few cases. In three cases Colebrook and Kenny observed cyanosis due to sulphemoglobinemia, but all recovered.

This work is still in the experimental stage, and needs to be confirmed. The number of patients who have been treated with these drugs is very small, and no series of cases has been adequately controlled. The possibility of serious untoward effects has not been excluded. It is, therefore, quite impossible to draw any definite conclusions as to the value of this treatment, but the results which have been reported seem sufficiently promising to warrant continued trial under conditions which permit accurate observation, together with adequate controls.

P. W. C.

REVIEWS

Principles of Biochemistry. By ALBERT P. MATHEWS, Andrew Carnegie Professor of Biochemistry, University of Cincinnati. x + 512 pages; 23.5 × 16.5 cm. William Wood and Company, Mt. Royal and Guilford Aves., Baltimore, Maryland. 1936. Price, $4.50.

Students of the biological sciences have long been acquainted with the author and his familiar and authoritative "Physiological Chemistry," since he has been teaching biochemistry to medical students and contributing to experimental research for forty years. The present volume, however, is shorter and written in a different style—in fact it is an entirely new book. It is written in six parts, namely, Glucides, Lipides and Proteins which constitute the major portion of the book, and Blood and Connective Tissues, Vitamins and Hormones, and Energy Metabolism. The approach to certain subjects, especially the discussion of the carbohydrates, proteins and fats, is somewhat unusual in that the description of their more fundamental chemical principles is smoothly blended with a discussion of the factors influencing their digestion and metabolism, both under normal and pathological conditions. A valuable addition to the subject matter is the discussion of clinical material.

Written in a most interesting manner, the book is very readable and is a good text to use along with the usual set of lectures which are given to medical students. This volume should be especially valuable to the student or young doctor preparing for the board examination, or to doctors or workers in science generally who wish to review and bring up-to-date their knowledge of biochemistry especially as it concerns the human body. The younger student with a flair for research will find its pages a veritable storehouse of enticing problems awaiting solution. The author states that he has omitted "almost all references to the literature as this is not intended to be a reference handbook." This the reviewer feels is to be regretted. The modern medical student is interested in the experimental development of biochemistry, but has had little if any training in consulting the original literature, and certainly receives insufficient assistance along this line while in medical school. It seems unfortunate that Dr. Mathews, with his great personal knowledge of the historical background of biochemistry, has not made this information available to the student by means of an organized bibliography. This defect, however, is insignificant in comparison with the general excellence of the book.

It was the purpose of the author to "correlate and synthesize the numerous facts, so that they will appear not as an inchoate assembly of facts, but as making part of a great science which reveals the finer structure and coördinated chemistry of the human body." This purpose, in the reviewer's mind, has been well attained.

E. G. S.

Textbook of Surgery. By JOHN HOMANS. 4th edition. 1267 pages; 25.5 × 17.5 cm. Charles C. Thomas, Springfield, Illinois, and Baltimore, Maryland. 1936. Price, $8.00.

Through its four editions since 1931, this book has kept the characteristics intended by its author, namely, an edited reflection of the teaching in the surgical department of the Harvard Medical School developed by Harvey Cushing and his associates. Accordingly it is an almost unique weld of the historical development of surgery, the dogmatism necessary for student teaching and present surgical beliefs.

The present edition differs from the third by the inclusion of chapters on Amputations and Plastic Surgery. This new material is well up to the standard of the remainder of the book.

E. M. H.

The Thyroid—Surgery, Syndromes, Treatment. By E. P. SLOAN, M.D. 475 pages; 26 × 17.5 cm. Published by Charles C. Thomas, Springfield, Illinois, and Baltimore, Maryland. 1936. Price, $10.00.

This book represents the experience and judgment derived from the observation of 20,000 patients in a thyroid clinic. Although the author states that the book is not intended to be encyclopedic, no phase of his subject has been neglected. The bibliography contains 254 names. The authors of the bibliography are indexed and there are indices of subjects and names. Chapters on the parathyroid glands and the thymus are also included.

In such a monograph there is necessarily much that a reviewer may find to which exception might be taken as to fact or interpretation of fact, but such disagreement in opinion in no way detracts from the value of this book. One might point out that recent work on the lymphatics of the thyroid could have been discussed with advantage in particular connection with some of the author's own ideas. Considerable emphasis is given to an unknown substance which for the purpose of discussion the author calls "thyrom," pictured as the active principle contained in the thyroxin molecule which differentiates thyroxin from iodin. The discussions of the underlying basis of symptoms is interesting. The chapters on surgical treatment are particularly complete with a well presented exposition of the surgical anatomy. In such a well finished production this reviewer regrets to see the use of such a hybrid as "subnormalcy" which the author uses in place of more acceptable wording.

This book will be found a valuable addition to the literature on thyroid disease.

E. M. H.

Modern Treatment of Diseases of the Respiratory System. By A. LISLE PUNCH, M.B., M.R.C.P.; and F. A. KNOTT, M.D., M.R.C.P., D.P.H. 295 pages; 14 × 20 cm.; illustrated. P. Blakiston's Son and Co., Inc., Philadelphia. 1936.

The authors as stated in the preface, have intended this book primarily for the general practitioner and the medical student who is just beginning his hospital training.

From this standpoint they have achieved their purpose admirably. The text is concise and yet comprises an adequate survey of the field of pulmonary disease. The authors have included painstaking descriptions of various clinical procedures, such as the technic of thoracentesis, pneumothorax, etc., and have included illustrations and descriptions of apparatus. The roentgenographic plates are exceedingly good and abundant, and the pathology is clearly pointed out, thus adding materially to the value of the book.

H. V. L.

The Diagnosis and Treatment of Diseases of the Peripheral Arteries. By SAUL S. SAMUELS, A.M., M.D. 260 pages; 51 illustrations; 22.25 × 15 cm. Indexed. Oxford University Press, New York. 1936. Price, $3.50.

This volume is not an exhaustive treatise on the subject matter of the title. A classification of diseases of the peripheral arteries is presented and methods of examination and diagnosis are described. Thromboangiitis obliterans is discussed at some length. The author considers the use of tobacco, especially cigarette smoking, to be a very important factor in the progress of the disease. He emphasizes his belief in the efficacy of intravenous hypertonic saline injections plus rest and postural exercises in the treatment of this condition, and finds most other methods that have been advocated to be of doubtful use or even harmful. There is very little discussion of the other methods of treatment. There is a briefer discussion of arteriosclerosis obliterans and diabetic gangrene. Very short chapters on Raynaud's disease, erythro-

melalgia and essential thrombophilia are included. There is also a chapter on the medico-legal aspects of peripheral arterial disease.

The reviewer does not feel that this book can be recommended as a well balanced discussion of the subject matter of the title. It does forcefully present the author's views on the treatment of thromboangiitis obliterans.

W. S. L.

Tuberculosis. By GERALD B. WEBB, M.D. 205 pages; 17 × 11.5 cm. Paul B. Hoeber, Inc., New York. 1936. Price, $2.00.

Dr. Webb's book is the first in the series of Clio Medica limiting itself exclusively to one disease entity and as such sets a noteworthy example for others that will surely follow. In dealing with this age-old disease, so intimately tied up with the history of medicine in general, Dr. Webb has divided the subject into its various phases. Practically every chapter takes up just one aspect of the subject of tuberculosis and discusses it in its entirety, chronologically. It is thus possible to get a complete picture of the history of any one phase of the disease by reading the appropriate chapter.

The few illustrations and charts are well chosen and the quotations extremely interesting. It might be worthwhile to translate some of the quotations which are presented in the original. The bibliography and the index of names increase the value of this book. This most recent contribution to the history of tuberculosis will be welcomed by all students of the disease. It is scholarly and informative and yet at the same time readable and entertaining.

M. S. S.

COLLEGE NEWS NOTES

Life Member

Dr. Samuel A. Vogel (Fellow), Buffalo, N. Y., has become a Life Member of the College under date of January 25, 1937.

Gifts to the College Library

The following gifts to the College Library of publications by members are gratefully acknowledged:

Books

Major Daniel B. Faust (Fellow), (MC), U. S. Army, one autographed book, "Diet Manual, Letterman General Hospital";
Dr. Jacob Gutman (Fellow), Brooklyn, N. Y.—9th Supplement to "New Modern Drugs";
Dr. J. J. Singer (Fellow) and Dr. Evarts A. Graham, F.A.C.S., St. Louis, Mo.—one autographed book, "Surgical Diseases of the Chest" (with Harry C. Ballon).

Reprints

Dr. Miles J. Breuer (Fellow), Lincoln, Nebr.—1 reprint;
Dr. E. H. Drake (Fellow), Portland, Maine—3 reprints;
Lt. Col. Frederick H. Foucar (Fellow), (MC), U. S. Army—1 reprint;
Dr. Salvatore Lojacono (Fellow), Tucson, Ariz.—1 reprint;
Dr. John H. Musser (Fellow), New Orleans, La.—27 reprints;
Dr. E. Sterling Nichol (Fellow), Miami, Fla.—7 reprints;
Dr. William H. Ordway (Fellow), Mount McGregor, N. Y.—3 reprints;
Dr. Carleton B. Peirce (Fellow), Ann Arbor, Mich.—13 reprints;
Dr. Horace K. Richardson (Fellow), Stockbridge, Mass.—3 reprints;
Dr. J. J. Singer (Fellow), St. Louis, Mo.—20 reprints;
Dr. Willard J. Davies (Associate), Rockville Centre, N. Y.—2 reprints;
Dr. Everett C. Fox (Associate), Dallas, Tex.—12 reprints;
Dr. Louis L. Perkel (Associate), Jersey City, N. J.—1 reprint.

Kentucky Members Held Annual Meeting

The Kentucky Fellows and Associates of the American College of Physicians held their annual meeting at Lexington, Ky., January 9, 1937. Dr. Ernest B. Bradley (Fellow), Lexington, President of the College, Dr. C. W. Dowden (Fellow), Louisville, College Governor for Kentucky, and Dr. J. W. Scott (Fellow), Lexington, Chairman for Arrangements, sponsored the meeting. Thirty-five members of the College were in attendance, in spite of extremely inclement weather. The afternoon program was as follows:

Dr. R. W. Sparkman (by invitation): "Quantitative Estimations of Glycosuria Following Intravenous Administration of Glucose";
Dr. R. B. Warfield (by invitation): "Calcinosis Universalis";
Dr. Ernest B. Bradley (Fellow): "An Unusual Type of Lymphosarcoma";
Dr. John Harvey (Fellow): "Contracted Kidneys Due to Pyelonephritis";
Dr. C. H. Fortune (Fellow): "Edema of Obscure Type."

In the evening a dinner was held at the LaFayette Hotel. The entire meeting has been reported as a very successful, beneficial and enjoyable one. The policies and practices of the College are more thoroughly understood by the members at large, members are given a closer contact with one another from the social angles of these local meetings, and interest is inspired in the activities of the College.

Dr. Henry W. Grote (Associate), Bloomington, Ill., has accepted an appointment as head of the Roentgenological Department of the Brokaw Hospital of Bloomington.

Mr. William Albert Widmer, head of the medical sales department of the J. B. Lippincott Company, publishers, died suddenly early in January. Mr. Widmer was known widely in the medical profession, because for many years his face was a familiar one at the book exhibits of the J. B. Lippincott Company at medical meetings all over the country. In fact, Mr. Widmer probably was the dean of medical exhibitors, for he was among the very first to initiate the plan of making conveniently available to doctors for examination books or other medical products by displaying them at the annual gatherings of various medical societies.

Mr. Theodore A. Phillips, for some years associated with the W. B. Saunders Company, publishers, has been appointed successor to Mr. Widmer, with the J. B. Lippincott Company.

Dr. John H. Musser (Fellow), New Orleans, was a guest speaker at a meeting of the San Diego (Calif.) Academy of Medicine, December 3.

The Stanford University School of Medicine, San Francisco, presents each winter a series of popular medical lectures, given on alternate Friday evenings. Among contributors to the fifty-fifth series now in progress were the following:

Dr. Benjamin W. Black (Fellow), Oakland, January 22, "The County Hospital and the Public";

Dr. William C. Voorsanger (Fellow), San Francisco, February 5, "Recent Advances in the Treatment of Tuberculosis."

Dr. Samuel A. Levine (Fellow), Boston, discussed "Pitfalls in the Diagnosis of Heart Disease" before a joint meeting of the Medical Society of the District of Columbia and the Washington Heart Association on December 9.

Dr. John W. Ferree (Associate), Bluffton, Ind., has been appointed chief of the recently created bureau of local health administration, Indiana State Division of Public Health.

Dr. Donald Gregg (Fellow), Wellesley, Mass., is President of the Massachusetts Society for Mental Hygiene.

On December 16, 1936 a meeting of the Rhode Island Fellows and Associates of the College was held at the John M. Peters House of the Rhode Island Hospital. At the meeting, Dr. Charles F. Gormly was elected Chairman, and Dr. Cecil Dustin, Secretary. Dr. Guy W. Wells was elected Chairman of a program committee of

four members: Dr. Wells, Dr. Alex. M. Burgess, Governor of the College for Rhode Island, and the Chairman and Secretary of the Rhode Island group, ex-officio. Dr. Jacob Fine of the Beth. Israel Hospital of Boston was the guest speaker of the occasion and gave an interesting account of experimental work on the effect, upon the absorption of gases in the body, of inhalation of concentrated oxygen mixtures.

Dr. Henry A. Christian (Fellow), Hersey Professor of the Theory and Practice of Physics at Harvard University Medical School will prepare and edit future revisions of Osler and McCrae's "The Principles and Practice of Medicine."

Dr. N. Thomas Saxl (Fellow), New York City, has been appointed Medical Director of the Police Athletic League, an organization formed by the Juvenile Aid Bureau of New York City, for the purpose of providing suitable physical and recreational activities for children with delinquent tendencies.

Dr. Henry Snure (Fellow) and Dr. George Maner presented a paper on "Roentgen-Ray Evidence of Metastatic Malignancy in Bone" before the Radiological Society of North America, on November 30, at Cincinnati, Ohio. Their exhibit illustrating their paper won first award in the scientific exhibits.

New Life Members

The following have become Life Members of the American College of Physicians on the dates indicated:

Dr. Manfred Kraemer, Newark, N. J.	January 9, 1937
Dr. James W. Hunter, Jr., Norfolk, Va.	January 9, 1937
Dr. Herbert B. Smith, Corning, N. Y.	January 11, 1937
Dr. Fresenius Van Nuys, Weston, Mass.	January 12, 1937
Dr. George M. Settle, Baltimore, Md.	January 12, 1937
Dr. Edward B. Vedder, Washington, D. C.	January 13, 1937
Dr. Robert A. Peers, Colfax, Calif.	January 16, 1937
Dr. Joseph Condit, Pasadena, Calif.	January 18, 1937
Dr. Charles W. Stone, Cleveland, Ohio	January 18, 1937

CONDENSED MINUTES OF THE BOARD OF REGENTS

Philadelphia, Pa.

December 13, 1936

The Board of Regents of the American College of Physicians met at its Philadelphia headquarters, 4200 Pine Street, at 10:00 a.m., December 13, 1936, with Dr. Ernest B. Bradley, President, presiding. The following were present:

Ernest B. Bradley, President
James H. Means, President-Elect
O. H. Perry Pepper, First Vice President
David P. Barr, Second Vice President
Walter L. Bierring, Third Vice President
William D. Stroud, Treasurer
William Gerry Morgan, Secretary-General
Sydney R. Miller

George Morris Piersol
Robert A. Cooke
Jonathan C. Meakins
Hugh J. Morgan
James E. Paullin
James Alex. Miller
Francis M. Pottenger
Maurice C. Pincoffs
Charles H. Cocke

and Mr. E. R. Loveland, Executive Secretary, acting as secretary of the meeting.

The Executive Secretary read abstracted Minutes of the Detroit meeting of the Board of Regents, which were approved as read. He then read in full the Minutes of the meeting of the Executive Committee held at Philadelphia on June 21, 1936.

Upon motion by Dr. James E. Paullin, seconded by Dr. George Morris Piersol, and regularly carried, it was

Resolved, that the Board of Regents approve of the action of the Executive Committee, and that their Minutes be adopted.

The Executive Secretary then presented the following communications:

(*a*) A letter from Dr. E. L. Tuohy, Governor for Minnesota, dated June 29, 1936, recommending the election of an additional Governor for the State of Minnesota, this additional Governor to take over the southern part of Minnesota and, perhaps, the State of South Dakota.

Discussion developed the opinion that it should be possible for Dr. Tuohy to obtain adequate information about candidates in southern Minnesota through members of the Mayo group in Rochester, and that it would be better to handle the situation in this way for the present time.

Upon motion by Dr. James E. Paullin, seconded by Dr. George Morris Piersol, it was

Resolved, that Dr. Tuohy's communication be acknowledged, and the suggestions concerning handling the Minnesota situation without an additional Governor be communicated to him.

(*b*) Following advice that the law required the College to have a Certificate of Authority as a Corporation foreign to the State of Pennsylvania to operate its main office in this State, proper steps had been taken to obtain an official Certificate of Authority from the State Department of Pennsylvania.

(*c*) Communications from the Social Security Board. Forms had been filled out and returned, with the explanation that the College is a Corporation organized "not for profit." Although no reply or decision had been received from the Social Security Board, the Executive Secretary expressed the opinion that the College would not be subject to the regulations of the Social Security Act.

(*d*) A communication from the U. S. Post Office granting a reclassification of the ANNALS OF INTERNAL MEDICINE, and reducing the mailing rates to 1½c per pound, resulting in a considerable saving in the future on postage.

President Bradley then presented a letter, dated July 23, 1936, from Dr. George Crile, Chairman of the Board of Regents of the American College of Surgeons. Dr. Crile asked whether it would be possible for the American College of Surgeons and the American College of Physicians to jointly consider a plan to eliminate the indiscriminate use of the words "Physician and Surgeon" by men without special training in a special field, and to have each doctor designated in his practice as "Physician," "Surgeon," "Medical Specialist," "Surgical Specialist" or "General

Practitioner." Dr. Crile suggested that the General Practitioner should limit his practice to diagnosis, medicine, minor surgery, emergency work and non-operative obstetrics; that the two Colleges should work together to influence the authoritative bodies to bring this change. Dr. Bradley had replied, stating that he had no authority to act, but that the matter would be referred to the Board of Regents, who might be disposed to appoint a committee to confer with a committee from the American College of Surgeons. A further communication from Dr. Crile indicated that such a committee had been appointed by his organization.

After general discussion, Dr. James Alex. Miller moved, and Dr. James E. Paullin seconded the following resolution, which was carried:

Resolved, that the President be authorized to appoint a committee of from one to three members to confer with a similar committee of the American College of Surgeons in any matters in which both bodies may be interested.

Dr. William Gerry Morgan, Secretary-General, reported the following deaths since the last meeting of the Board of Regents:

Master:		
Anders, James M.	Philadelphia, Pa.	August 29, 1936
Fellows:		
Ackerman, James F.	Asbury Park, N. J.	August 5, 1936
Atwell, Jacob C.	Butler, Pa.	November 2, 1936
Brooks, Harlow	New York, N. Y.	April 13, 1936
Brundage, Albert H.	Woodhaven, N. Y.	March 12, 1936
Chase, Arthur B.	Oklahoma City, Okla.	July 20, 1936
Dearman, William A.	Whitfield, Miss.	November 4, 1936
DeLaney, Matthew A.	Carlisle, Pa.	November 1, 1936
Gordon, Thomas D.	Grand Rapids, Mich.	November 20, 1936
Haines, Charles J.	Hallstead, Pa.	November 3, 1936
Hastings, Gordon Lee	Little Rock, Ark.	September 14, 1936
Hinton, Charles C.	Macon, Ga.	February 25, 1936
Holmes, Arthur D.	Detroit, Mich.	February 20, 1936
Johnson, Gertrude M.	Battle Creek, Mich.	January 29, 1936
Klotz, Oskar	Toronto, Ont., Canada	November 3, 1936
Manges, Willis F.	Philadelphia, Pa.	November 24, 1936
Marchbanks, Howard E.	Pittsburg, Kan.	August 7, 1936
Marriott, W. McKim	San Francisco, Calif.	November 11, 1936
Mayer, William H.	Pittsburgh, Pa.	August 23, 1936
Murray, Peter	New York, N. Y.	March 6, 1936
Pierce, Alano E.	Minot, N. D.	March 14, 1936
Quintard, Edward	New York, N. Y.	February 12, 1936
Reyher, Christopher M.	Gary, Ind.	February 12, 1936
Simon, Sidney K.	New Orleans, La.	August 5, 1936
Simonds, Clarence E.	Willimantic, Conn.	April 1, 1936
Spear, Robert	East Chicago, Ind.	August 23, 1936
Stern, Arthur	Elizabeth, N. J.	November 28, 1936
Stoll, Henry F.	Hartford, Conn.	September 28, 1936
Synnott, Martin J.	Montclair, N. J.	July 15, 1936
Thompson, Edward G.	Memphis, Tenn.	June 21, 1936
Williams, Alden H.	Grand Rapids, Mich.	June 10, 1936
Wilson, John D.	Scranton, Pa.	June 20, 1936
Associates:		
Moll, Carl F.	Flint, Mich.	May 1, 1936
Quigley, William J.	Cleveland, Ohio	March 8, 1936
Smith, Webster S.	Dayton, Ohio	January 30, 1936

President Bradley stated that he would appoint a committee later on to draw up suitable memorials for those who had been past presidents or governors of the College.

The following memorial prepared by Dr. S. Marx White was read by the Secretary-General, Dr. Morgan, and a resolution adopted providing that it be spread upon the Minutes of the Board of Regents and a copy sent to Dr. Brown's widow:

GEORGE E. BROWN

"Dr. George Elgie Brown was born at Grand Rapids, Michigan, July 16, 1885. He received the degree of M. D. in 1909 from the University of Michigan, following which he served two years' internship at the Northern Pacific Hospital, Brainerd, Minnesota. He was married to Irma Parker, July 12, 1911. During the years of his practice in internal medicine at Miles City, Montana, from 1911 to 1921, he carried on special studies at Harvard University for five months in 1914, studied organic chemistry in the summer of 1916 at Johns Hopkins University, Baltimore, and was with the Rockefeller Foundation in France in 1918 and 1919. He was appointed first assistant in medicine at the Mayo Clinic, Rochester, Minnesota, February 1, 1921, and made an associate in medicine, April 1, 1922, later becoming head of a section in medicine at the Mayo Clinic, and associate professor of medicine, in the Mayo Foundation, University of Minnesota. He filled these appointments with distinction until his death. Fellow of the American Medical Association and of the American College of Physicians, he was a member of the Board of Regents of the College from 1927 to 1933. He was also a member of the American Society of Clinical Investigation, the Central Society for Clinical Research, the Alumni Association of the Mayo Foundation, the Association of American Physicians, the Central Inter-urban Clinical Club, the Minnesota Society of Internal Medicine and the Southern Minnesota Medical Association. He was a member of Phi Rho Sigma fraternity and of Sigma XI honorary fraternity.

"During the two years' internship in Brainerd and the ten years of practice in Miles City, he exhibited unusual initiative and industry in clinical research. His first paper, entitled 'The Practical Use of Tuberculin in Diagnosis,' was published in 1911 as a result of work done during his internship. Ten more papers, the majority of them in first-class journals, were published during the ten years of active practice in Montana. During these latter years also he was known to have exhibited much ingenuity in the construction of x-ray apparatus for his own use in practice. During the period of nearly fifteen years of association with the Mayo Clinic, the contributions to medical literature bearing his name or as co-author number 115. His contributions revealed marked originality and by them he became one of the leading authorities in this country, particularly in diseases of the vascular system and in arterial hypertension. His standard cold-pressor test for measuring variability in blood pressure, published with E. A. Hines, Jr., and his contributions with several members of the Mayo Clinic staff have served to break new paths in the ready recognition of hyper-reactors in essential hypertension and in the surgical treatment of certain of the later stages of the disorder. The 200-page monograph on thromboangiitis obliterans bearing his name is of great practical value in that it serves to show that correct diagnoses can be made without special methods in more than 95 per cent of the cases of the vascular diseases affecting the extremities. His initiative and drive, his helpful, cheerful friendliness and practical, wise counsel will be greatly missed not only in the organizations to which he gave the best years of his life, but also by an almost unlimited number of friends and by the American College of Physicians.

—S. MARX WHITE, M.D., F.A.C.P."

The Secretary-General then reported the following additional Life Members since the last meeting:

Carl Herman Gellenthien, Valmora, N. M.
Herman O. Mosenthal, New York, N. Y.
Orville H. Brown, Phoenix, Ariz.
Roy L. Leak, Middletown, Conn.

making a total of sixty-four Life Members.

Dr. James E. Paullin, Chairman of the Committee on Public Relations, reported that his committee had examined into the correspondence and circumstances of the following resignations, which, by resolution of the Board of Regents, were accepted:

Fellows:

Dr. Arthur F. Cooper, Memphis, Tenn.
Dr. William J. Young, Louisville, Ky.

Associates:

Colonel Glenn I. Jones (Retired), M. C., U. S. Army
Dr. Ernest L. Kiesel, Scranton, Pa.

The Committee had received a communication from the late Dr. James M. Anders (Master) concerning the establishment of a National Health Day. Since this topic of health education is already so well covered by local, state and public health organizations, the Committee merely recommended coöperation with these groups.

The Committee felt that an appeal from the American Association for China Famine and Flood Relief was without the purposes of the College, and recommended no action.

The Committee recommended that the facilities of the American College of Physicians be placed at the disposal of the Council on Medical Education of the American Medical Association for the promotion of residencies in internal medicine in approved hospitals, and that the College express itself as being in sympathy with attempts to develop better training in the field of internal medicine and its related specialties.

On motion by Dr. O. H. Perry Pepper, seconded by Dr. William D. Stroud, and regularly carried, it was

Resolved, that the recommendations by the Committee on Public Relations be approved.

Reporting as a committee of one, Dr. James H. Means submitted the following suggested revision of the Fellowship Pledge, in accordance with a resolution adopted by the Board of Regents at one of its Detroit meetings:

"Appreciating that the American College of Physicians has been created to foster the noblest principles and traditions of our calling, and having voluntarily accepted membership therein, I solemnly pledge that I will live in conformity with its ideals and regulations to the best of my ability.

"Especially do I dedicate myself to practice medicine following the Golden Rule and the good precepts of the Oath of Hippocrates; to place ever before my own, the welfare of patients dependent upon my professional knowledge and skill; to respect the interest and character of my colleagues; to supplement, as occasion requires, my own judgment with the wisdom and council of competent medical specialists; to render assistance willingly to my colleagues; to extend freely my professional aid to the unfortunate, the poor and the needy; to seek constant increase in medical knowledge through reading of authoritative literature and by attendance at important gatherings of my professional brethren, by study with physicians of eminence, and by free exchange of experience and opinion with my colleagues.

"Further, I promise to refrain from seeking the public eye for purposes of self-advancement; to avoid commercialism in all my professional activities; to adjust my fees to the circumstances of my patients and to make them commensurate with the services I have rendered.

"Moreover, I hereby condemn and promise to avoid all abasing money trades with brother practitioners or consultants, and I hereby swear that I will strive constantly to spread among all physicians with whom I come in contact a high ethic of practice like that set forth in the Constitution and By-Laws of the American College of Physicians."

Upon motion by Dr. Means, seconded by Dr. Barr, and regularly carried, it was *Resolved*, that the above Fellowship Pledge be approved in the place of the one heretofore used.

Dr. Maurice C. Pincoffs, as Editor of the ANNALS OF INTERNAL MEDICINE, presented a brief report upon the editorial work on the journal.

Dr. O. H. Perry Pepper, as Chairman of the House Committee of the College, reported that the new headquarters had been purchased for $52,500, and after paying incidental expenses in connection with the transfer of title, settlement, etc., the Committee had a balance remaining of $2,142.75 of the original appropriation for the purchase of the property at 4200 Pine Street, Philadelphia. Of the $10,000.00 appropriated for alterations and furnishings, $4,500 approximately had been spent on alterations, and $4,500 approximately on furnishings, leaving a balance of $929.16. There had been certain expenditures for taxes, additional insurance, etc., which had been charged against this appropriation, but which Dr. Pepper felt should be charged to some other account, as a matter of bookkeeping. He described the alterations and furnishings that had been completed, and the proposed plan for future operation. In appreciation to Mr. Charles J. Eisenlohr, from whom the property was purchased, Dr. Pepper moved the adoption of the following resolution, which was regularly seconded and unanimously carried:

Resolved, that the Officers and Regents of the American College of Physicians extend to Mr. Charles J. Eisenlohr the thanks of the College for his many courtesies incident to the purchase from him of the new College Headquarters and also for his generous gift of various beautiful furnishings, including andirons, draperies, safe cabinet, billiard table, and other valuable items.

Dr. Sydney R. Miller, Chairman of the Committee on Credentials, reported that of 91 names presented for Fellowship, either by promotion from Associateship or directly, 80 were recommended for election; 5 were recommended for election first as Associates; 3 were rejected; and 3 were deferred for further investigation. 186 names had been presented for Associateship, of which 152 were recommended for election; 21 were rejected; and 13 deferred. The names of those recommended for election, both to Fellowship and Associateship, were inspected by the Regents.

Upon motion by Dr. George Morris Piersol, seconded by Dr. James E. Paullin, and regularly carried, it was

Resolved, that the following list of 55 be and herewith are elected to Fellowship in the American College of Physicians as of this date, December 13, 1936.

Candidates	*Sponsors*
CALIFORNIA	
Morris Henry Nathanson, Los Angeles (formerly of Minnesota)	Henry L. Ulrich, S. Marx White, J. B. Carey, E. L. Tuohy.
CONNECTICUT	
Marcus Backer, Bridgeport	Daniel P. Griffin, Charles H. Sprague, Henry F. Stoll (deceased).
Henry Caplan, Meriden	Thomas P. Murdock, William E. Hall, George Blumer.

Candidates	*Sponsors*
MEDICAL CORPS, U. S. NAVY	
Robert Edwin Duncan, Washington, D. C.	Lyle J. Roberts, Robert G. Davis, P. S. Rossiter.
Jesse Bundren Helm, Newport, R. I.	W. W. Hall, Paul F. Dickens, P. S. Rossiter.
Daniel Hunt, Annapolis, Md.	Louis H. Roddis, S. S. Cook, P. S. Rossiter.
Howard Howlett Montgomery, Washington, D. C.	O. J. Mink (deceased), C. R. Baker, P. S. Rossiter.
Lloyd Russell Newhouser, Annapolis, Md.	C. R. Baker, Louis H. Roddis, P. S. Rossiter.
Harold Eugene Ragle, Washington, D. C.	Lyle J. Roberts, Paul F. Dickens, P. S. Rossiter.
Clarence Wesley Ross, Washington, D. C.	Louis H. Roddis, E. R. Stitt, P. S. Rossiter.
Robert Franklin Sledge, Washington, D. C.	Paul F. Dickens, W. W. Hall, P. S. Rossiter.
William Henry Hart Turville, Portsmouth, Va.	C. R. Baker, G. E. Thomas, P. S. Rossiter.
Paul White Wilson, Washington, D. C.	E. R. Stitt, Lyle J. Roberts, P. S. Rossiter.
U. S. PUBLIC HEALTH SERVICE	
Thomas Parran, Washington, D. C.	Thomas A. Groover, Oscar B. Hunter, Wallace M. Yater.
FLORIDA	
Warren Wilson Quillian, Coral Gables	P. B. Welch, George L. Cook, T. Z. Cason.
Mathew Jay Flipse, Miami	P. B. Welch, Kenneth Phillips, T. Z. Cason.
E. Sterling Nichol, Miami	P. B. Welch, Kenneth Phillips, T. Z. Cason.
GEORGIA	
Jack Clayton Norris, Atlanta	John B. Fitts, H. C. Sauls, Glenville Giddings.
Roy Rachford Kracke, Emory University	Joseph Yampolsky, Trimble Johnson, Glenville Giddings.
Samuel Frederick Rosen, Savannah	J. Reid Broderick, Lee Howard, Glenville Giddings.
ILLINOIS	
Grant Harrison Laing, Chicago	Joseph L. Miller, George H. Coleman, Arthur R. Elliott, James G. Carr.
Lowell Delford Snorf, Chicago	Charles A. Elliott, Arthur E. Mahle, James G. Carr.
IOWA	
Frederick William Mulsow, Cedar Rapids	Jeannette Dean-Throckmorton, John H. Peck, Fred M. Smith.
MASSACHUSETTS	
Erwin Hartwell Taylor, Pittsfield	William Henry Watters, Sara M. Jordan, William B. Breed.
MICHIGAN	
Charles Vernon Crane, Grand Rapids	Abel J. Baker, Burton R. Corbus, Henry R. Carstens.
George Courtney Stucky, Lansing	L. G. Christian, Milton Shaw, Henry R. Carstens.
MINNESOTA	
Ragnvald S. Ylvisaker, Minneapolis	Edwin L. Gardner, Archie H. Beard, E. L. Tuohy.

Candidates	*Sponsors*
	MISSOURI
Paul Forrey Stookey, Kansas City	D. D. Stofer, Harry L. Jones, A. C. Griffith.
Anthony Bigelow Day, St. Louis	Walter Baumgarten, Howard A. Rusk, A. C. Griffith.
Llewellyn Sale, St. Louis	Harry L. Alexander, Ralph Kinsella, David P. Barr, A. C. Griffith.
	MONTANA
John Paul Ritchey, Missoula	Allen R. Foss, Wybren Hiemstra, Louis H. Fligman.
	NEBRASKA
Frederick Wilhelm Niehaus, Omaha	Rodney W. Bliss, Lynn T. Hall, Adolph Sachs.
	NEW JERSEY
Joseph Wiener, Asbury Park	W. G. Herrman, C. A. Pons, Clarence L. Andrews.
Henry Charles Crossfield, East Orange	Walter G. Lough, A. Wilbur Duryee, Robert A. Cooke, Clarence L. Andrews.
	NEW YORK
Roy Lorraine Scott, Buffalo	Nelson G. Russell, Clayton W. Greene, Allen A. Jones.
William Herbert Ordway, Mount McGregor	Lawrason Brown, J. Burns Amberson, Jr., Grant Thorburn, Allen A. Jones, Walter W. Palmer.
Benjamin I. Ashe, New York	Herman O. Mosenthal, Milton A. Bridges, Walter W. Palmer.
Zacharias Bercovitz, New York	A. Wilbur Duryee, Irving S. Wright, Walter W. Palmer.
Maurice Coleman Harris, New York	Samuel Weiss, Robert Chobot, Robert A. Cooke.
Walter Roger Scott, Niagara Falls	Edward C. Koenig, Clayton W. Greene, Allen A. Jones.
Edwin Philip Russell, Rome	William S. McCann, Lester Betts, David P. Barr, Allen A. Jones.
Isaac Shapiro, Schenectady	Lester Betts, Frank vander Bogert, Robert A. Cooke.
	NORTH CAROLINA
John Alexander Shaw, Fayetteville	W. T. Rainey, P. P. McCain, C. H. Cocke.
	OHIO
Edward Harvey Cushing, Cleveland	J. M. Hayman, Jr., Charles T. Way, William D Stroud, A. B. Brower.
Edward Winfield Miskall, East Liverpool	Fred B. Wilson, R. R. Snowden, E. Bosworth McCready, A. B. Brower.
	OKLAHOMA
Cad Walder Arrendell, Ponca City	Carroll M. Pounders, Douglas M. Gordon, Lea A. Riely.
	OREGON
Leon Albert Goldsmith, Portland	John H. Fitzgibbon, Laurence Selling, T. Homer Coffen.
	PENNSYLVANIA
Laurence Coleman Milstead, Allentown	Henry I. Klopp, Francis J. Dever, E. J. G. Beardsley.

Candidates	*Sponsors*
	RHODE ISLAND
Clifton Briggs Leech, Providence	Charles F. Gormly, Herman A. Lawson, Alexander M. Burgess.
Elihu Smith Wing, Providence	Charles F. Gormly, Samuel A. Levine, Alexander M. Burgess.
	TEXAS
James Howard Park, Jr., Houston	M. L. Graves, Alvis E. Greer, C. T. Stone.
George Washington Parson, Texarkana	Bayard T. Horton, E. V. Allen, C. T. Stone.
	TERRITORY OF HAWAII
Nils Paul Larsen, Honolulu	W. W. Boardman, Ernest S. duBray, James F. Churchill.
	CANADA
	New Brunswick
Arthur Brittan Walter, St. John	Hugh A. Farris, R. H. M. Hardisty, D. Sclater Lewis.
	Ontario
Ross Martin Lymburner, Hamilton	F. A. Willius, J. H. Holbrook, Jabez H. Elliott.

Resolved, that the following list of 24 candidates be and herewith are elected to Fellowship as of April 18, 1937, due to the fact that their three-year minimum Associate period does not expire until that time.

Candidates	*Sponsors*
	ARIZONA
Redford Alexander Wilson, Tucson	S. C. Davis, Charles S. Kibler, W. Warner Watkins.
	CALIFORNIA
Frederick Samuel Modern, Los Angeles	E. Richmond Ware, Roland Cummings, James F. Churchill.
	DISTRICT OF COLUMBIA
William Phillip Argy, Jr., Washington	Matthew White Perry, Paul F. Dickens, Wallace M. Yater.
	INDIANA
Horace McMurran Banks, Indianapolis	Larue D. Carter, Edgar F. Kiser, Robert M. Moore.
	KENTUCKY
John Richard Gott, Jr., Louisville	Hugh R. Leavell, John Walker Moore, C. W. Dowden.
Maurice Gray Buckles, Waverly Hills	J. Murray Kinsman, Morris Flexner, C. W. Dowden.
	LOUISIANA
Edgar Hull, New Orleans	Clyde Brooks, Ben R. Heninger, J. E. Knighton.
Carlo Joseph Tripoli, New Orleans	Clyde Brooks, Ben R. Heninger, J. E. Knighton.
	MASSACHUSETTS
Lyman Howard Hoyt, Boston	Henry A. Christian, Elliott P. Joslin, William B. Breed.
Alexander Marble, Boston	F. Gorham Brigham, Walter Bauer, William B. Breed.

Candidates	*Sponsors*
	MICHIGAN
Carleton Barnhart Peirce, Ann Arbor	Cyrus C. Sturgis, Carl V. Weller, Henry R. Carstens.
John Vincent Fopeano, Battle Creek	Margaret Bell, W. M. Brace, Henry R. Carstens.
William S. Reveno, Detroit	Frederick G. Buesser, Richard M. McKean, Henry R. Carstens.
	MINNESOTA
Oren Leslie Kirklin, Rochester	A. R. Barnes, Austin C. Davis, E. L. Tuohy.
	NEBRASKA
John Marshall Neely, Lincoln	George W. Covey, F. L. Rogers, Adolph Sachs.
	NEW YORK
Leonard M. Niesen, Livingston	Harry A. Pattison, Lawrason Brown, James Alex. Miller, Walter W. Palmer.
	OHIO
Bruce Kenneth Wiseman, Columbus	Charles A. Doan, Walter M. Simpson, A. B. Brower.
Edward Everett Campbell, Columbus	John Dudley Dunham, E. F. McCampbell, A. B. Brower.
	PENNSYLVANIA
George Booth, Pittsburgh	Frank A. Evans, C. C. Wholey, E. Bosworth McCready.
	RHODE ISLAND
Jacob E. Greenstein, Providence	John F. Kenney, Charles F. Gormly, Alex. M. Burgess.
	TENNESSEE
Henry Clay Long, Knoxville	Robert B. Wood, E. R. Zemp, J. O. Manier.
	TEXAS
Samuel Ainslie Shelburne, Dallas	D. W. Carter, Jr., J. Shirley Sweeney, C. T. Stone.
	VIRGINIA
Alfred Brownley Hodges, Norfolk	F. C. Rinker, Frank H. Redwood, J. Morrison Hutcheson.
	WISCONSIN
Annette Clarke Washburne, Madison	J. S. Evans, William S. Middleton, Rock Sleyster.

Resolved, that the following 157 candidates be and herewith are elected to Associateship in the American College of Physicians.

ELECTIONS TO ASSOCIATESHIP

Candidates	*Sponsors*
	ALABAMA
Joe Hollis Little, Mobile	E. S. Sledge, Daniel T. McCall, Fred W. Wilkerson.
	ARIZONA
Zebud MacKay Flinn, Prescott	Earle Wood Phillips, Frank J. Milloy, W. Warner Watkins.

Candidates	*Sponsors*
ARKANSAS	
John Herman Baird (U. S. V. A.), North Little Rock	Philip B. Matz, Charles M. Griffith, Oliver C. Melson.
CALIFORNIA	
Oran Idnire Cutler, Loma Linda	Newton Evans, Percy T Magan, James F. Churchill.
Donald E. Griggs, Los Angeles	R. Manning Clarke, Percy T. Magan, James F. Churchill.
Elliott Plummer Smart, Olive View	Edward W. Hayes, Robert L. Cunningham, James F. Churchill.
John Carl Schlappi, San Diego	William H. Barrow, R. H. Sundberg, James F. Churchill.
Albert Howell Elliot, Jr., Santa Barbara	Franklin R. Nuzum, W. D. Sansum, James F. Churchill.
Richard Donald Evans, Santa Barbara	Franklin R. Nuzum, W. D. Sansum, James F. Churchill.
Harrie Augustus Patterson (U. S. V. A.), West Los Angeles	M. K. Wylder, L. S. Peters, H. S. Cumming, Charles M. Griffith.
COLORADO	
Raymond James Savage, Denver	W. Bernard Yegge, Clough Turrill Burnett, Gerald B. Webb.
Alfred Martin Wolfe, Denver	W. Bernard Yegge, Lorenz W. Frank, Gerald B. Webb.
CONNECTICUT	
Lee D. van Antwerp, Meriden	Thomas P. Murdock, Cole B. Gibson, George Blumer.
Morris Albert Hankin, New Haven	Theodore S. Evans, S. J. Goldberg, George Blumer.
DELAWARE	
Gerald Aloysius Beatty, Wilmington	B. M. Allen, W. H. Kraemer, Lewis B. Flinn.
MEDICAL CORPS, U. S. NAVY	
Irwin Louis Vincent Norman, Chelsea, Mass.	Louis H. Roddis, E. V. Allen, P. S. Rossiter.
U. S. PUBLIC HEALTH SERVICE	
William Hyatt Gordon, Fort Stanton, N. M.	Carl Mulky, M. K. Wylder, L. S. Peters.
DISTRICT OF COLUMBIA	
James Wallace Esler, Washington	Matthew White Perry, W. A. Bloedorn, Wallace M. Yater.
Henry B. Gwynn, Washington	Thomas S. Lee, Matthew White Perry, Wallace M. Yater.
Edward Patrick McLarney, Washington	Frank Leech, E. Clarence Rice, Wallace M. Yater.
FLORIDA	
James Louden Borland, Jacksonville	R. H. McGinnis, Louie Limbaugh, T. Z. Cason.
L. Sydnor Laffitte, Jacksonville	R. H. McGinnis, Louie Limbaugh, T. Z. Cason.
J. Webster Merritt, Jacksonville	R. H. McGinnis, Louie Limbaugh, T. Z. Cason.

Candidates	*Sponsors*
	GEORGIA
Mark Stovall Dougherty, Jr., Atlanta	Joseph Yampolsky, Trimble Johnson, Glenville Giddings.
William Hugh Trimble, Atlanta	Joseph Yampolsky, Trimble Johnson, Glenville Giddings.
Richard Hugh Wood, Atlanta	John Baker Fitts, H. C. Sauls, Glenville Giddings.
Francis Power Parker, Emory University	Joseph Yampolsky, Trimble Johnson, Glenville Giddings.
Thomas Llewellyn Ross, Jr., Macon	Joseph Yampolsky, Trimble Johnson, Glenville Giddings.
William P. Harbin, Jr., Rome	Joseph Yampolsky, Trimble Johnson, Glenville Giddings.
James Clayton Metts, Savannah	J. Reid Broderick, Lee Howard, Glenville Giddings.
	ILLINOIS
M. Herbert Barker, Chicago	N. S. Davis, III, Clifford J. Barborka, James G. Carr.
Faris Franklin Chesley, Chicago	George H. Coleman, Arthur R. Elliott, James G. Carr.
Israel Davidsohn, Chicago	Philip B. Matz, Oscar B. Hunter, James G. Carr.
Samuel Glenwood Plice, Chicago	Laurence E. Hines, David E. Markson, James G. Carr.
Herbert Albert Sacks, Chicago	A. A. Goldsmith, Charles A. Elliott, James G. Carr.
Emil George Vrtiak, Chicago	Ernest E. Irons, Sidney A. Portis, James G. Carr.
Michael Zeller, Chicago	Harold A. Rosenbaum, Josiah J. Moore, James G. Carr.
Harry Allen Richter, Evanston	H. A. McGuigan, N. S. Davis, III, James G. Carr.
Richard Hale Young, Evanston	A. C. Ivy, Arthur E. Mahle, James G. Carr.
Douglas Boyd, Highland Park	David E. Markson, N. S. Davis, III, James G. Carr.
Harry W. Shuman, Rock Island	B. J. Cronwell, H. A. Beam, Samuel E. Munson.
	KANSAS
James Abram Butin, Chanute	Howard E. Marchbanks (deceased), William C. Menninger, Thomas T. Holt.
George Arthur Westfall, Halstead	P. T. Bohan, Henry N. Tihen, Thomas T. Holt.
Arthur Joseph Revell, Pittsburg	William C. Menninger, Ralph M. Fellows, Thomas T. Holt.
Kenneth Lewis Druet, Salina	Henry N. Tihen, Harold W. Palmer, Thomas T. Holt.
John Lewis Kleinheksel, Wichita	Henry N. Tihen, E. V. Allen, Thomas T. Holt.
	KENTUCKY
Edward Cornelius Humphrey, Louisville	J. Murray Kinsman, H. V. Noland, C. W. Dowden.
Archibald Donaldson Kennedy, Louisville	J. Murray Kinsman, H. V. Noland, C. W. Dowden.
Woodford Bates Troutman, Louisville	Sam A. Overstreet, John Walker Moore, C. W. Dowden.
	LOUISIANA
Stanley George Wolfe, Shreveport	Marion D. Hargrove, Clarence H. Webb, J. E. Knighton.
	MAINE
Donald Howard Daniels, Portland	E. H. Drake, Mortimer Warren, E. W. Gehring

Candidates	*Sponsors*
	MARYLAND
Robert W. Garis, Baltimore	Thomas P. Sprunt, Walter A. Baetjer, Henry M. Thomas, Jr.
Francis Wilcox Gluck, Baltimore	Louis P. Hamburger, Walter A. Baetjer, Henry M. Thomas, Jr.
Charles Franklin Mohr, Baltimore	Walter A. Baetjer, Thomas P. Sprunt, Henry M. Thomas, Jr.
David Tenner, Baltimore	Louis Krause, John E. Legge, M. C. Pincoffs.
Perry Franklin Prather, Hagerstown	Victor F. Cullen, R. S. Stauffer, Henry M. Thomas, Jr.
	MASSACHUSETTS
Earle MacArthur Chapman, Boston	F. Dennette Adams, B. H. Ragle, William B. Breed.
Greene Fitz Hugh, Boston	Maurice Fremont-Smith, Albert A. Hornor, William B. Breed.
James Carlin McAdams, Fall River	William Mason, Charles C. Wolferth, J. H. Means, William B. Breed.
	MICHIGAN
Herman Marvin Pollard, Ann Arbor	Cyrus C. Sturgis, Frank N. Wilson, Henry R. Carstens.
Henry Barthell Steinbach, Detroit	Rollin H. Stevens, Hugo A. Freund, Henry R. Carstens.
Martin Hugh Hoffmann, Eloise	William J. Stapleton, Jr., Henry A. Luce, Henry R. Carstens.
John Doyle Littig, Kalamazoo	Cyrus C. Sturgis, Arthur C. Curtis, Henry R. Carstens.
Leland E. Holly, Muskegon	William M. LeFevre, Lawrence Reynolds, Henry R. Carstens.
Edward Kupka, Pontiac	William H. Gordon, George A. Sherman, James D. Bruce.
Richard Ellsworth Olsen, Pontiac	Harold R. Roehm, George A. Sherman Henry R. Carstens.
	MINNESOTA
Thomas Williams Baker, Rochester	F. A. Willius, E. V. Allen, E. L. Tuohy.
Thomas Jan Dry, Rochester	F. A. Willius, E. V. Allen, E. L. Tuohy.
Grace Arabell Goldsmith, Rochester	E. V. Allen, Henry W. Woltman, E. L. Tuohy.
John Harold Mills, Rochester	Russell M. Wilder, E. V. Allen, E. L. Tuohy.
Hendrik Marinus Rozendaal, Rochester	H. Z. Giffin, Charles H. Watkins, E. L. Tuohy.
Jan Henrik Tillisch, Rochester	P. S. Hench, P. G. Boman, E. L. Tuohy.
	MISSISSIPPI
Douglas Davison Baugh, Houston	Felix J. Underwood, J. M. Bamber, G. W. F. Rembert.
	MISSOURI
Herbert J. Rinkel, Kansas City	L. P. Gay, William W. Duke, A. C. Griffith.
Sim F. Beam, St. Louis	Walter Baumgarten, Howard A. Rusk, A. C. Griffith.
Kenneth F. Glaze, St. Louis	Walter Baumgarten, Charles Hugh Neilson, A. C. Griffith.
Harold Gould Newman, St. Louis	Howard A. Rusk, Walter Baumgarten, David Barr, A. C. Griffith.
David Miller Skilling, Jr., St. Louis	Howard A. Rusk, Walter Baumgarten, David Barr, A. C. Griffith.

Candidates	*Sponsors*
	MONTANA
Ellis K. Giere, Fort Peck	Jay C. Davis, S. Marx White, Louis H. Fligman.
Malcolm Duncan Winter, Miles City	Allen R. Foss, Wybren Hiemstra, Louis H. Fligman.
	NEBRASKA
Karl W. Brimmer, McCook	G. L. Pinney, A. F. Tyler, Adolph Sachs.
Augustus David Cloyd, Omaha	Rodney W. Bliss, Warren Thompson, Adolph Sachs.
Chester Quay Thompson, Omaha	Rodney W. Bliss, John R. Kleyla, Adolph Sachs.
	NEW JERSEY
Robert Brannan Durham, Atlantic City	Hilton S. Read, William W. Fox, Clarence L. Andrews.
Richard Dabney Anderson, Burlington	Marcus W. Newcomb, Thomas Fitz-Hugh, Jr., Clarence L. Andrews.
Jerome George Kaufman, Newark	Aaron E. Parsonnet, Edgar Mayer, Clarence L. Andrews.
Benjamin Saslow, Newark	Manfred Kraemer, Charles E. Teeter, Clarence L. Andrews.
Sigurd Walter Johnsen, Passaic	Anthony Bassler, Samuel Weiss, Clarence L. Andrews.
Louis Francis Albright, Spring Lake	William G. Herrman, C. A. Pons, Clarence L. Andrews.
	NEW YORK
George W. Weber, Albany	Frederic W. Holcomb, F. H. Voss, Walter W. Palmer.
George B. Dorff, Brooklyn	Maurice J. Dattelbaum, Harry R. Litchfield, Walter W. Palmer.
Herman Tarnower, Brooklyn	J. Burns Amberson, Jr., Henry H. Haft, Walter W. Palmer.
Ramsdell Gurney, Buffalo	Nelson G. Russell, A. H. Aaron, Allen A. Jones.
Frank Meyers, Buffalo	A. H. Aaron, Francis D. Leopold, Allen A. Jones.
Stuart L. Vaughan, Buffalo	Nelson G. Russell, A. H. Aaron, Allen A. Jones.
Alan Ramseur Anderson, Freeport	Irving Sherwood Wright, Arthur Freeborn Chace, Walter W. Palmer.
Arthur Julian Horton, Hollis	Carl Boettiger, Charles M. Levin, Goodwin A. Distler, Robert A. Cooke.
LeMoyne Copeland Kelly, New York	R. Garfield Snyder, Lewis A. Conner, Walter W. Palmer.
Ralph Horton, Oneonta	Max Pinner, J. Burns Amberson, Jr., Robert A. Cooke.
Meyer S. Rednick, Ossining	Arthur F. Heyl, Warren F. Kahle, Walter W. Palmer.
Preston Hepburn Watters, Rochester	William S. McCann, Charles B. F. Gibbs, Allen A. Jones.
George Johnson, Staten Island	Alexis T. Mays, Edward E. Cornwall, Walter W. Palmer.
Clement Joseph Handron, Troy	Crawford R. Green, James F. Rooney, Robert A. Cooke.
Alson J. Hull, Troy	Crawford R. Green, Harry W. Carey, Robert A. Cooke.

Candidates	*Sponsors*
North Carolina	
Merle Dumont Bonner, Jamestown	D. Waldo Holt, P. W. Flagge, C. H. Cocke.
Erle B. Craven, Jr., Lexington	Harold L. Amoss, Robert L. Felts, C. H. Cocke.
David Edman Quinn (U. S. V. A.), Oteen	Philip B. Matz, Charles M. Griffith, C. H. Cocke.
Ohio	
Ian Bruce Hamilton, Canton	Charles A. LaMont, Casper H. Benson, A. B. Brower.
Louis Nicholas Jentgen, Columbus	Charles A. Doan, John Dudley Dunham, A. B. Brower.
Phillip T. Knies, Columbus	Charles A. Doan, John Dudley Dunham, A. B. Brower.
Myron D. Miller, Columbus	Charles A. Doan, Casper H. Benson, A. B. Brower.
Oklahoma	
Elbert Henderson Shuller, McAlester	T. H. McCarley, Henry H. Turner, Lea A. Riely.
Coyne Herbert Campbell, Oklahoma City	Henry H. Turner, L. J. Moorman, Lea A. Riely.
Pennsylvania	
Willard Daniel Kline, Allentown	Henry I. Klopp, Francis J. Dever, E. J. G. Beardsley.
William J. Armstrong, Butler	J. C. Atwell (deceased), Lester Hollander, E. Bosworth McCready.
John W. Shadle, Butler	J. C. Atwell (deceased), R. R. Snowden, E. Bosworth McCready.
Thomas A. Johnson, Drexel Hill	Thomas Klein, Joseph T. Beardwood, Jr., George Morris Piersol.
David L. Perry, New Castle	Wayne W. Bissell, Eliah Kaplan, E. Bosworth McCready.
Albert Warner Dewey, Philadelphia	Winfred Dana, George C. Griffith, George Morris Piersol.
Maurice Spencer Jacobs, Philadelphia	David Riesman, Joseph C. Doane, E. J. G. Beardsley.
John H. Willard, Philadelphia	H. L. Bockus, Russell S. Boles, E. J. G. Beardsley.
Wilfred Derwood Langley, Sayre	Stanley D. Conklin, C. H. DeWan, E. J. G. Beardsley.
Hyman A. Slesinger, Windber	Elwood W. Stitzel, H. B. Anderson, E. Bosworth McCready.
Rhode Island	
Francis Hasseltine Chafee, Providence	Guy W. Wells, Charles F. Gormly, Alexander M. Burgess.
Frank Bryant Cutts, Providence	Guy W. Wells, Charles F. Gormly, Alexander M. Burgess.
Morgan Cutts, Providence	Guy W. Wells, Herman A. Lawson, Alexander M. Burgess.
Cecil Calvert Dustin, Providence	Guy W. Wells, Charles F. Gormly, Alexander M. Burgess.
John Church Ham, Providence	Herman A. Lawson, Guy W. Wells, Alexander M. Burgess.

Candidates	*Sponsors*
	TENNESSEE
Philip Henry Levinson, Chattanooga	Leopold Shumacker Franklin B. Bogart, J. O. Manier.
Charles Leroy Denton, Dyersburg	Otis S. Warr, William C. Chaney, J. O. Manier.
Edward Guy Campbell, Memphis	Otis S. Warr, William C. Chaney, J. O. Manier.
William Frazier Dobyns (U. S. V. A.), Memphis	Charles M. Griffith, E. J. Rose.
Henry B. Gotten, Memphis	Otis S. Warr, William C. Chaney, J. O. Manier.
Joseph Franklin Hamilton, Memphis	Otis S. Warr, Conley H. Sanford, J. O. Manier.
	TEXAS
Leslie McKnight Smith, El Paso	Orville E. Egbert, C. M. Hendricks, C. T. Stone.
John Arthur Alvarez, Houston	F. R. Lummis, George Herrmann, C. T. Stone.
William Henry Cade, San Antonio	Lee Rice, Robert M. Barton, C. T. Stone.
	UTAH
Richard Francis McLaughlin, Price	O. J. LaBarge, L. E. Viko, G. Gill Richards.
William C. Walker, Salt Lake City	Otis Wildman, Frederick Ceres, George Morris Piersol.
	VIRGINIA
John Braxton McKee, Winchester	Dean B. Coie, R. Finley Gayle, Jr., J. Morrison Hutcheson
	WASHINGTON
John Wylie Skinner, Kirkland	James M. Bowers, George C. Miller, C. E. Watts.
John Kay Martin, Seattle	George C. Miller, James M. Bowers, C. E. Watts.
Donald Ainslie Palmer, Spokane	George H. Anderson, Arthur Betts, C. E. Watts.
Max Singer Wright, Spokane	George H. Anderson, Arthur Betts, C. E. Watts.
Walter Cyril Nalty (U. S. V. A.), Walla Walla	E. L. Whitney, Bryan M. Riley, C. E. Watts, Charles M. Griffith.
	WEST VIRGINIA
Frederick Rendell Whittlesey, Morgantown	G. R. Maxwell, Charles M. Bray, John N. Simpson, Walter E. Vest.
Frank J. Holroyd, Princeton	Albert H. Hoge, Walter E. Vest, John N. Simpson.
	WISCONSIN
Charles Everard Lyght, Madison	J. S. Evans, William S. Middleton, Rock Sleyster.
Benjamin J. Birk, Milwaukee	Andrew I. Rosenberger, John Huston, Rock Sleyster.
	TERRITORY OF HAWAII
Carl John Walfrid Wilen, Hilo	H. L. Arnold, A. G. Schnack, James G. Carr.
Stewart Edward Doolittle, Honolulu	H. L. Arnold, A. G. Schnack, C. E. Watts.
Richard D. Kepner, Honolulu	H. L. Arnold, A. G. Schnack, David Barr.
Kyuro Okazaki, Honolulu	Edward L. Bortz, George C. Griffith, George Morris Piersol.
	CANADA
	British Columbia
Samuel Edward Caldbick Turvey, Vancouver	J. C. McMillan, D. M. Baltzan, Fred T. Cadham.
	New Brunswick
William Oswald McDonald, St. John	H. A. Farris, Colin G. Sutherland, D. Sclater Lewis.
	Ontario
Trenholm Lawrence Fisher, Ottawa	Warren S. Lyman, Arthur T. Henderson, Jabez H. Elliott.
	Republic of Panama
Amadeo Vicente-Mastellari, Panama	Tomás Guardia, C. D. Briscoe, William M. James.

Dr. Sydney R. Miller then brought up the request of some Mexican candidates who had applied for the privilege of paying their initiation fee and dues in Mexican dollars, which are worth less than one-third of the equivalent in American currency. If the dues of Mexican members were accepted in Mexican dollars, the proceeds would be less than one-half the expenses of carrying such members on the Roster.

Upon motion by Dr. O. H. Perry Pepper, seconded by Dr. William D. Stroud, and regularly carried, it was

Resolved, that members of the College in foreign countries, including Mexico, shall pay their fees and dues in American currency.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, reported that his Committee had found it desirable to choose the candidates for the Research Fellowship of the College at the autumn meeting of the Regents, rather than at the Annual Meeting. Seven excellent applicants had been given very careful consideration. The Committee recommended that the Research Fellowship for 1937–38 be awarded to Dr. Robert Wallace Wilkens, now of Boston, Mass., for a year entirely devoted to research with Dr. E. Arnold Carmichael at the National Hospital, Queens Square, London, England.

Upon motion by Dr. James Alex. Miller, seconded by Dr. William D. Stroud, and regularly carried, it was

Resolved, that a Research Fellowship of the American College of Physicians, amounting to $1,800.00 and available beginning July 1, 1937, be awarded to Dr. Robert Wallace Wilkens.

The Committee on Fellowships and Awards further recommended that the John Phillips Memorial Award be given to Dr. Richard E. Shope of the Rockefeller Institute for Medical Research, Princeton, N. J.

Upon motion by Dr. David P. Barr, seconded by Dr. Jonathan C. Meakins, and regularly carried, it was

Resolved, that the 1937 Award of the John Phillips Memorial Medal be made to Dr. Richard E. Shope.

Dr. Barr reported that the Committee feels there is much room for profitable extension of the granting of Fellowships, and that this would afford one of the useful applications of the funds of the College.

Dr. James H. Means, Chairman of the Committee on the ANNALS OF INTERNAL MEDICINE, had no report to add to that already made by the Editor. He added, however, that the Committee would recommend to the Board of Regents that Dr. Paul Clough be officially appointed Assistant Editor of the ANNALS.

Upon motion by Dr. James H. Means, seconded by Dr. Robert A. Cooke, it was

Resolved, that the Board of Regents confirm the official appointment of Dr. Paul Clough, of Baltimore, as Assistant Editor of the ANNALS OF INTERNAL MEDICINE.

Dr. Jonathan C. Meakins, Chairman of the Committee on Constitution and By-Laws, reported that his Committee had taken under consideration certain changes which should be recommended as amendments to the Constitution and By-Laws of the College.

PROPOSED AMENDMENTS TO THE CONSTITUTION

Article IV, " (*a*) Fellows. Fellows shall be members of the medical profession engaged as practitioners, teachers or research workers in Internal Medicine, who shall have been elected. . . ."

(change consists of the omission of " or in an allied specialty ")

Article V, " Section 1. Associates shall be members of the medical profession engaged as practitioners, teachers or research workers in Internal Medicine, who shall have been elected. . . ."

(change consists of the omission of " or in an allied specialty ")

On motion by Dr. James Alex. Miller, seconded by Dr. William D. Stroud, and regularly carried, it was

Resolved, that the Board of Regents approve of the amendments to the Constitution above outlined, and that notice of the proposal for these amendments shall be published in the ANNALS OF INTERNAL MEDICINE in accordance with the requirements of the Constitution, Article VI.

PROPOSED AMENDMENTS TO THE BY-LAWS

Article V, "Section 1. . . . (*a*) He shall be more than 33 years of age;"

(change consists of a change in the age from 29 to 33)

"(*c*) He shall be a member in good standing in his local, state and national medical societies, except in the case of those not engaged in practice, such as full-time teachers or research workers in Internal Medicine;"

(change consists of elimination of "etc." and substituting "in Internal Medicine")

Article V, Section 2, line 6, eliminate "or by an Officer of the College, or by a member of the Board of Regents."

"Section 3. (*a*) In the case of practitioners without teaching or important hospital positions, or of candidates not engaged in the practice of Clinical Medicine, the candidate's nomination shall be accompanied by all necessary information as to fitness, by a satisfactory thesis, or by publications of sufficient number and character to qualify him for Fellowship."

(this is practically entirely reworded)

Note—In regard to outstanding persons in pathology, pharmacology, biochemistry, etc., these may be consider eligible under Article V, Section 3 (*c*), second paragraph, which should read as follows:

"After 1931, a candidate for Fellowship shall be eligible only if already an Associate, except upon the high recommendation of the Committee on Credentials by reason of outstanding merit and accomplishment."

(this change consists of the rewording of the paragraph)

Article VI, "Section 1. He shall possess a Certificate from the American Board of Internal Medicine as having passed successfully the examinations of that Board."

(this is the insertion of an entirely new paragraph, entailing relettering the succeeding paragraphs—the present paragraph (*a*) becoming "(*b*)"; (*b*) becoming "(*c*)"; (*c*) becoming "(*d*)"; (*d*) becoming "(*e*)"; and (*e*) becoming "(*f*)")

Article VI, Section 1, old paragraph (*c*), new paragraph "(*d*) . . . except in the case of those not engaged in practice, such as full-time teachers and research workers in Internal Medicine."

(this change consists of eliminating "those holding official hospital positions, etc." and substituting "in Internal Medicine")

Article VI, Section 1, old paragraph (*d*), new paragraph "(*e*)," line 6, ". . . in Internal Medicine or in medical research."

(this change consists of the above substitution for "in one of the accepted branches of Internal Medicine or in Medical Research")

Speaking on the proposed changes to the By-Laws, Dr. Meakins said the Committee had been faced with the problem of whether it should recommend changes requiring candidates to have passed successfully the examination of the American Board of Internal Medicine. There were three alternatives:

(1) To make successful passage of the examination a prerequisite for Associateship;
(2) To make successful passage of the examinations a prerequisite to Fellowship;
(3) To ignore it altogether.

The Committee felt that it would be better to make successful passage of the examinations a prerequisite to Associateship. This would assure the College that candidates for Associateship will have shown evidence of proper training, ethical standing, affiliations, etc., and would avoid the anomaly of admitting a candidate to Associateship who might later fail to pass the examination.

Upon motion by Dr. James Alex. Miller, seconded by Dr. George Morris Piersol, and regularly carried, it was

Resolved, that the above proposed amendments to the By-Laws be submitted in writing to all members of the Board of Regents before its next meeting.

In the discussion of the proposed amendments to the By-Laws, there was divergence of opinion among Board members as to whether the requirement of certification by the American Board of Internal Medicine should precede Associateship, or be one of the requirements between Associateship and Fellowship. Several felt that Associates should be admitted much on the same plan as at present, with the exception of the amendment in the minimum age, but that before such an Associate may be eligible for Fellowship, he must obtain the certification of the American Board of Internal Medicine. By inserting this requirement between Associateship and Fellowship, the Committee on Credentials may eliminate the requirement of presenting case histories and autopsies, which have not proved a particularly satisfactory criterion in the past.

Dr. Meakins, in discussing the underlying principles leading to the recommendation for amendments, in his report said, "In practically all the statements in the present Constitution and By-Laws, there is left considerable latitude as to research workers, laboratory workers, roentgenologists and the comprehensive term of an 'allied specialty.' A primary duty of the Credentials Committee is to review presented evidence, which would indicate that a candidate is sufficiently trained to practice Internal Medicine of a standard acceptable to the College. Whether, in the future, he should become engaged in hospital administration, medical research, roentgenology, etc., should not influence his future standing in the College. On the contrary, if his main activities have been for years in any of these branches of medical practice, no matter how high his reputation and accomplishments in these or other branches of medical practice, which are not directly concerned with the practice of Internal Medicine, they should not in any way justify his selection as an Associate of the College."

Dr. Charles H. Cocke, Chairman of the Board of Governors, inquired whether the Committee on Constitution and By-Laws had prepared any recommendation in regard to the appointment of alternate Governors.

Dr. Meakins replied that his Committee had only considered the eligibility of candidates, but would take care of some provision for alternate Governors later on.

Dr. Meakins asked for the opinion of the Board of Regents on a suggestion that there be created a group to be known as Emeritus Fellows, consisting of those who may retire, more or less, from the activities of the College on account of age.

During the discussion of the matter, the reaction seemed favorable, though no specific resolution was adopted.

Dr. Walter L. Bierring, Chairman of the American Board of Internal Medicine, presented the following report:

"The initiative for the formation of a certifying board for internists originated with the action of the American College of Physicians at the meeting of the Board of Regents in Philadelphia, April 30, 1935. At the meeting the Board of Regents voted to underwrite the organization expense of said Board up to the sum of $10,000.00.

"Concurrent action in the organization of the American Board of Internal Medicine was taken by the Section on the Practice of Medicine of the American Medical Association meeting in executive session at Atlantic City, June 14, 1935.

"A joint Committee of Organization was formed comprising five representatives approved by President James Alex. Miller from the American College of Physicians, Meakins, Pepper, Barr, Richards, and Middleton, and four representatives, appointed by Chairman William J. Kerr from the Section on the Practice of Medicine of the American Medical Association, Fitz, Irons, Musser and Bierring, the latter was chosen as Chairman of the Joint Committee.

"This Committee made its first report to the Board of Regents of the American College of Physicians at the meeting in Philadelphia, December 14, 1935, presenting a preliminary draft of the Constitution and By-Laws with an outline of the plan of examination and certification procedure.

"The Articles of Incorporation of the American Board of Internal Medicine were filed for record on the 28th day of February, 1936.

"At the meeting of the Board of Regents in Detroit, March 2, 1936, the organization of the American Board of Internal Medicine was officially approved and an appropriation of $5,000.00 was voted to defray the expenses of the Board during the first year. At the meeting of the American Medical Association in Kansas City, May 12 and 13, 1936, the Board was given the final approval by the Section on the Practice of Medicine of the American Medical Association, the Advisory Board for Medical Specialties, and the Council on Medical Education and Hospitals of the American Medical Association.

"With this final action, the American Board of Internal Medicine was duly organized and ready to begin operation.

"The first meeting of the Board was held at the Palmer House, Chicago, June 14 and 15, 1936, at which the final details of organization were completed. The officers chosen for the first year were, Chairman, Walter L. Bierring; Vice Chairman, Jonathan C. Meakins; Secretary-Treasurer, O. H. Perry Pepper; Assistant Secretary-Treasurer, P. M. Hutchinson, Attorney.

"The terms of tenure of service of the members of the Board, as provided by the Articles of Incorporation, were determined by lot as follows:

Representing the American College of Physicians:

Dr. Jonathan C. Meakins	1 year
Dr. G. Gill Richards	1 year
Dr. O. H. Perry Pepper	2 years
Dr. William S. Middleton	2 years
Dr. David P. Barr	3 years

Representing the Section on the Practice of Medicine of the American Medical Association:

Dr. Reginald Fitz	1 year
Dr. Ernest E. Irons	2 years
Dr. John H. Musser	3 years
Dr. Walter L. Bierring	3 years

"Attention is directed to Sections 5 and 7 of Article V of the Articles of Incorporation, which is as follows:

". . . the membership of the Board shall be maintained at the ratio of five members from the American College of Physicians and four members from the Section on the Practice of Medicine of the American Medical Association and that at least three of the members of the Board from the American College of Physicians and two members of the Board from the Section on the Practice of Medicine of the American Medical Association shall be of professorial rank in approved medical schools of the United States or Canada."

Section 5, Article V, Articles of Incorporation.

"The term of office of members of the Board succeeding the original Board members shall be three years and until their successors are elected and qualified, and no such member shall serve more than two consecutive three-year terms."

Section 7, Article V, Articles of Incorporation.

"The following committees were named:

Credentials and Qualifications

Dr. Jonathan C. Meakins, *Chairman*
Dr. William S. Middleton
Dr. Ernest E. Irons
Dr. Reginald Fitz

Examinations

Dr. David P. Barr, *Chairman*
Dr. O. H. Perry Pepper
Dr. G. Gill Richards
Dr. John H. Musser

"It was further decided at this meeting that the central office of the Board be maintained, for the present, at the office of the Chairman at 406 Sixth Avenue, Des Moines, Iowa.

"During the months of July and August, 1936, in accordance with the directions of the Board, a publicity statement regarding the American Board of Internal Medicine, presenting its object and purposes with an outline of the special training and method of examination required of candidates for certification was released to 75 different medical journals, including the Annals of Internal Medicine, Journal of the American Medical Association, Canadian Medical Association Journal, British Medical Journal, all State Medical Society Journals, and special journals. The statement was published complete or in abstract in practically all of the Journals submitted, and quite a number added favorable editorial comment.

"More complete information regarding the Board was later published in the form of a handbook.

"The second meeting of the Board was held in Chicago, October 11 and 12, 1936, at which time the date for the first written examination was set for Monday, December 14, 1936, in different cities throughout the United States, and wherever possible, to be at or near the place where the applicant resides. The written examination shall consist of two parts:

A. A three-hour examination upon subjects in anatomy, physiology, pharmacology, pathology, biochemistry, bacteriology, and immunology, which are related to the proper understanding of Internal Medicine. This shall be held at 9:00 o'clock, a.m., on the day of the examination.

B. A three-hour clinical examination of a general character to be held at 2:00 o'clock, p.m., on the day of the examination.

"The fees for examination have been set as follows:

For Written and Practical Examination	$40.00
For Certificate	10 00
For Certification without Examination	10.00

"At this meeting the following amendment to Article VI of the By-Laws, pertaining to special certification, was adopted:

"To amend Article VI by striking out all of Article VI and substituting the following:

ARTICLE VI

Special Certification

Advisors to the Board

Section 1. *A.* There shall be appointed to the Board a group of leading internists, not to exceed two hundred and fifty (250) in number, who shall be known as Advisors to the Board. They shall be certified without examination and their duties shall be to assist and advise the Board in the selection of Founders, the holding of examinations and such other duties as the Board may require of them.

B. They shall be selected by the Board as the Board may decide.

Founders

Section 2. Until July 1, 1937, certificates of the American Board of Internal Medicine will be issued without examination to a limited number of specialists in Internal Medicine approved by the Board from the following:

A. Professors and associate professors of medicine in approved schools of medicine of the United States and Canada.

B. Physicians who have practiced the specialty of Internal Medicine for ten years, and are members or Fellows in good standing in one or more of the following special societies of internal medicine:

1. American College of Physicians
2. Royal College of Physicians of Canada
3. Association of American Physicians
4. American Clinical and Climatological Association
5. American Gastro-enterological Association
6. American Society for Clinical Investigation
7. Central Society for Clinical Research

C. Physicians who have practiced the specialty of Internal Medicine for fifteen years, and who are recommended by the Executive Committee of the Section on the Practice of Medicine of the American Medical Association.

"It was moved that the Advisors to the Board be selected from the following:

1. Professorial heads of departments of Internal Medicine of all the approved medical schools of the United States and Canada. No such individual shall be eligible who is not an internist.
2. Emeritus and active members of the Association of American Physicians who are internists.

3. The officers and members of the Board of Regents for the year 1936–37 of the American College of Physicians who are internists.
4. The Advisors to the Board must be 45 years of age or over, except those chosen under paragraph No. 1 above.
   The Advisors to the Board shall be certified without examination upon the payment of the regular certification fee of $10.00.
5. An original member of the American Board of Internal Medicine shall, ipso facto, be certified without examination. On termination of his membership on the Board he shall automatically become an Advisor to the Board.

"It was the opinion of the Board that the Founders should be selected from applications addressed to the Board rather than from invitations sent out by the Board from a prepared list. It was decided that the following letter be sent to prospective Founders:

"'The American Board of Internal Medicine, organized through the coöperation of the American College of Physicians and the Section on the Practice of Medicine of the American Medical Association, may issue a certificate of qualification without examination to a limited number of specialists, according to Section 2, Article VI of its By-Laws as follows:

Section 2. Until July 1, 1937, certificates of the American Board of Internal Medicine will be issued without examination to a limited number of specialists in Internal Medicine, approved by this Board from the following:

A. Professors and Associate Professors of Internal Medicine in approved schools of medicine of the United States and Canada.

B. Physicians who have practiced the specialty of Internal Medicine for ten years, and are members or Fellows in good standing in one or more of the following special societies of Internal Medicine:

1. American College of Physicians
2. Royal College of Physicians of Canada
3. Association of American Physicians
4. American Clinical and Climatological Association
5. American Gastro-enterological Association
6. American Society for Clinical Investigation
7. Central Society for Clinical Research

C. Physicians who have practiced the specialty of Internal Medicine for fifteen years, and who are recommended by the Executive Committee of the Section on the Practice of Medicine of the American Medical Association.

"'As all others must pass an examination it seems but reasonable to the Board that those who are admitted without examination should show evidence of qualifications equivalent, or better, to that which the Board requires of those who apply for admission through examination.

"'The Board will give consideration to those who graduated or took their internship prior to the date of the establishment of the present standards of the Council on Medical Education and Hospitals of the American Medical Association.

"'If you are desirous of submitting your name you are requested to fill out the enclosed form and return to the office of the Chairman in the enclosed envelope

for consideration by the Board as to your eligibility for certification without examination.

"'A registration fee of $10.00 must accompany this application.'

"In conformity with the action of the Board at its last meeting on October 11–12, 1936, the list of Advisors to the Board was completed as selected from the following, in accordance with the method previously stated:

1. Professorial heads of departments of Internal Medicine of all approved medical schools of the United States and Canada.
2. Emeritus and active members of the Association of American Physicians.
3. Officers and members of the Board of Regents for the year 1936–37 of the American College of Physicians who are internists.

All Advisors to be 45 years of age or over, except those chosen as professorial heads of departments of Internal Medicine.

This list comprised 188 names. An individually signed letter was sent to each Advisor selected of the form adopted at the last meeting. The response was very gratifying as 168 favorable replies were received, each expressing interest in the purpose of the Board and appreciation for the selection. Eight of the Advisors selected had retired from active practice and preferred not to serve. Of the remaining 160, all but 6 have remitted the registration fee of Ten Dollars."

(Dr. Bierring at this point presented the list of Advisors.)

"The selection of a Founders list has not progressed as rapidly. Letters of the form adopted at the last meeting have been mailed to 1,500 Fellows of the American College of Physicians during the past week. Each letter was signed personally by the Chairman and an application enclosed for certification without examination, a statement of qualifications required of candidates taking the examination, and a business return envelope.

"Letters are now being prepared for members and Fellows of the following societies, who are not Fellows of the American College of Physicians or Advisors of the Board:

1. Royal College of Physicians of Canada
2. Association of American Physicians
3. American Clinical and Climatological Association
4. American Gastro-enterological Association
5. American Society for Clinical Investigation
6. Central Society for Clinical Research

"In addition, the professorial heads of Internal Medicine, who are Advisors, have been asked to submit a corrected list of professors and associate professors of Internal Medicine in their respective schools, and answers have been received from all, with a few exceptions.

"The entire list of Founders to be considered will probably comprise 2,500 names.

"The preparations for the first written examination on December 14, have proceeded in accordance with the plans adopted by the Board at the last meeting. Advisors of the Board have been assigned to serve as supervisors of the examination in the different cities with two exceptions—Bismarck, N. D., and Orlando, Fla. (In Bismarck, N. D., the State Health Officer, Dr. Maysil Williams will act as supervisor; and in Orlando, Fla., Dr. Meredith Mallory, F.A.C.P., will act in a similar capacity.)

"In each instance the candidate has been assigned a registration number, which will be retained throughout all the examinations, and directed by telegram to report at the designated place of examination on Monday, December 14, 1936, at 9:00 o'clock, a.m. A copy of this telegram is sent to the supervisor concerned for purposes of identification.

"A set of examination questions of Part 1 and Part 2 has been sent to each supervisor in separately sealed envelopes by special delivery mail. A supply of blank examination paper arranged in booklets has also been sent to each supervisor.

"The directions for conducting the written examination as submitted to each supervisor are as follows:

"'The examination will be in charge of the Advisor selected by the Board, who will observe the following directions and regulations:

1. Hold the examination on the day and hour prescribed.
2. Admit to the examination only those candidates who hold letter of admission from the Board.
3. Ascertain that the identification number given by each candidate, which is to be used on all of the answer papers, corresponds with the number assigned by the Board.
4. Break the seal of the question papers in the presence of the candidate at the beginning of each session of the examination.
5. Collect the answer papers after each session and at the close of the examination period, enclose these with identification forms, unused examination paper and questions, in addressed envelopes, and forward by express, collect, to the office of the Chairman, Room 1210, 406 Sixth Avenue, Des Moines, Iowa, U. S. A.'"

(Dr. Bierring stated at this point that there had been 53 candidates approved for admission to the first written examination, and gave the assignment of candidates with respect to the cities and examiners throughout the United States.)

"The Committee on Credentials and Qualifications did not approve eight applicants, because of insufficient qualifications. Each of the applicants was refunded $30.00 of the examination fee; $10.00 being retained as the registration fee.

"Four applicants having paid the examination fee of $40.00, upon further review by the Committee were recommended for certification without examination, and a refund will be made of $30.00 each. Three applications submitted for certification without examination, previously considered by the Board and resubmitted to the Committee on Credentials and Qualifications, were subsequently recommended for reference to the Executive Committee of the Section on the Practice of Medicine of the American Medical Association for further action. These have been forwarded as directed, but to date have not been returned.

"Four applications have been received to date for the second written examination to be held during March, 1937.

"The amount received by the Chairman for registration and examination fees, to date, is $4,310.15, of which $250.00 has been refunded, leaving a balance of $4,060.15 deposited in the Bankers Trust Company Bank, Des Moines, Iowa, to the account of the American Board of Internal Medicine, Walter L. Bierring, Chairman. It is to be noted that fees collected are to a certain extent a liability held in escrow until all examinations and certification procedure have been completed.

"All current expenses of the Board are paid out of the allotment of $5,000.00 granted by the American College of Physicians. Up to and including November 30, $3,761.12 has been expended. The estimated expense of this meeting and of current

expenses to and including December 31, 1936, is $875.00, making a total of $4,636.12, leaving an approximate balance January 1, 1937, of $363.88.

"In view of the increasing volume of work connected with the present operation of the Board and two meetings in prospect, April and June, 1937, it is estimated that at least $3,000.00 will be required to carry on until July 1, 1937. By this date it is reasonable to anticipate a considerable fund will be available from fees retainable.

"At the meeting of the American Board of Internal Medicine on December 12, 1936, the Chairman was directed, on behalf of the Board, to make application to the Board of Regents of the American College of Physicians for an additional grant of $3,000.00 to be available to June 30, 1937; it being understood that this grant of $3,000.00 in addition to the former grant of $5,000.00 is to be considered as a loan to the American Board of Internal Medicine to be refunded as soon as definite funds are available."

In conclusion, Dr. Bierring, on behalf of the American Board of Internal Medicine, thanked the Board of Regents for the wise counsel and financial aid which had been extended.

On motion by Dr. James Alex. Miller, seconded by Dr. James E. Paullin, and regularly carried, it was

Resolved, that the Board of Regents of the American College of Physicians express their appreciation of the progress that has been made by the American Board of Internal Medicine; and that the College approve the appropriation of the further amount of $3,000.00.

Dr. William D. Stroud submitted the following report, as Treasurer:

"Investments in Bonds, approximately	$80,000.00
Investments in Preferred Stocks	4,427.00
Investments in Common Stocks	15,500.00
Uninvested Cash in Endowment Fund	527.00
Cash in General Fund	27,977.00

"About $1,500.00 had been received from closed banks in Pittsburgh on account during the past year.

"The total assets, including investments, cash and the College Headquarters, approximate $183,000.00."

On motion by Dr. James Alex. Miller, seconded by Dr. James E. Paullin, and regularly carried, it was

Resolved, that the report of the Treasurer be accepted and filed. Dr. James Alex. Miller made a detailed report for the Finance Committee:

"The analysis of the Girard Trust Company of our securities was considered, and it was voted to approve the recommendations of their report.

"It was voted to withdraw our savings account and to invest it at some such good time in income bearing securities, after receiving recommendations from the Girard Trust Company, which would be circulated to the members of the Finance Committee.

"It was recommended that the Board of Regents approve the expenditures for taxes and insurance on the new headquarters as an item of upkeep, amounting to $1,109.63, which temporarily had been drawn from the funds appropriated for purchase and furnishings.

"It was recommended that the Board of Regents set up a repair and replacement fund, which it was suggested should amount to $500.00 a year.

"We would report that according to the estimate of the upkeep for 1937 in the new headquarters, the upkeep expenses will be $3,480.00, and that the capital outlay, $62,000.00 at 4 per cent interest, would be $2,480.00, so that the total upkeep and rental for the new headquarters would be approximately $6,000.00 a year.

"The Finance Committee considered in detail the 1937 budget presented by Mr. E. R. Loveland in behalf of various departments, and recommends it for approval

by the Regents as submitted, with estimated receipts of $77,500.00 and estimated expenditures of $60,257.67; an estimated balance of $17,242.33.

Respectfully submitted,

JAMES ALEX. MILLER, *Chairman,*
Committee on Finance"

Upon motion by Dr. Francis M. Pottenger, seconded by Dr. William Gerry Morgan, and regularly carried, it was

Resolved, that the report of the Finance Committee be approved, and the Committee authorized to make the sales and purchases recommended; further that the Treasurer be authorized to withdraw the funds from the savings accounts, and to invest the funds in securities to be approved by the Finance Committee; further that the Board of Regents approve the expenditures for taxes, insurance, etc., on the new headquarters, amounting to $1,109.63, and that this appropriation be added to the original appropriations for 1936; further that the Board of Regents approve the setting up of a repair and replacement fund of $500.00 per year—this amount merely being set aside if needed, but not otherwise withdrawn from invested funds; further that the detailed budgets recommended by the Finance Committee for 1937, with estimated receipts of $77,500.00 and estimated expenditures of $60,257.67, be approved.

Dr. Ernest B. Bradley, President, outlined the plans for the St. Louis Session, April 19–23, 1937, so far as the General Program and Convocation were concerned. Dr. David P. Barr, General Chairman, discussed the tentative program for the clinics, and Mr. Loveland, Executive Secretary, reported upon the business arrangements. Almost all the available exhibit space has been disposed of and all details have been arranged with the headquarters' hotel, the New Jefferson.

Dr. James Alex. Miller, Chairman, presented a report of progress for the Committee on Future Policy for the Development of Internal Medicine. This Committee had considered the comparative value of the John Phillips Memorial Award; the advisability of inviting speakers and lecturers from abroad and from the United States to give lectures under the auspices of the College and at its expense; and the idea of establishing a revolving fund to help younger practitioners to meet the requirements for registration as internists. The Committee had also considered the possibility of maintaining a directory of postgraduate activities to be published in the ANNALS.

No action had been taken on any of these suggestions.

Dr. James Alex. Miller also brought up the situation concerning the National Conference on Nomenclature of Disease. He stated that the Conference had published a Nomenclature of Disease which is now widely used, and which meets with wide approval. Through some oversight, an invitation to the College to participate in this work had not been accepted by the College in the year 1929. On behalf of the Chairman of the Executive Committee of the National Conference, Dr. Miller renewed the invitation to the College to coöperate with the long list of associations comprising the Conference.

Dr. Miller moved that the College lend its name in coöperation to the National Conference on Nomenclature of Disease.

This was seconded by Dr. William D. Stroud, and regularly carried.

On motion by Dr. George Morris Piersol, seconded by Dr. Walter L. Bierring, and regularly carried, it was

Resolved, that the College make an appropriation of $1,000.00 for the aid of this worthy work.

On motion by Dr. William D. Stroud, seconded by Dr. Sydney R. Miller, it was moved that the American College of Physicians establish another Research Fellowship of $1,800.00 for one year, July, 1937, to June, 1938.

In the discussion of the motion, it was agreed that the action was not to establish two Fellowships permanently, that in some years there might be more and in other years possibly none. The motion was carried.

On the recommendation of Dr. David P. Barr, on behalf of the Committee on Fellowships and Awards, by a motion made, seconded and regularly carried, it was

Resolved, that this Fellowship be awarded to Dr. Abner McGehee Harvey, now of the Johns Hopkins Hospital, Baltimore, Md.

In the absence of Dr. James D. Bruce, Chairman, Dr. Jonathan C. Meakins reported for the Committee on College Records of Members. The Committee, utilizing the form now in use in connection with the publication of the annual Directory, suggested an appropriate form which by resolution was adopted.

Dr. James Alex. Miller, on behalf of Dr. Walter W. Palmer, Governor for eastern New York; Dr. Luther F. Warren, Regent; Dr. Robert A. Cooke, Regent; and himself as Regent, presented the following invitation for the 1938 Annual Session of the College to be held in New York City:

> "We, the officers of the American College of Physicians, who reside in New York City, desire to request the favorable consideration of the Board of Regents of an invitation to hold the meeting of the College in 1938 in New York City.
>
> "Preliminary inquiries have established the fact that we would be able to obtain suitable hotel and auditorium facilities here and also that we would have the whole-hearted coöperation of the large medical centers for the presentation of the clinical programme.
>
> "The situation in New York is not one that lends itself to the usual method of presentation of an invitation for a meeting of the College, that is, it is not customary for organizations such as the County Medical Society, the Academy of Medicine or individual hospitals to invite medical organizations to meet in New York City. Consequently, we are asking you to consider this invitation as representing the hearty feeling of the Fellows of the College in New York City and of the principal hospital and educational institutions which would participate in the meeting.
>
> Very respectfully yours,
>
> (Signed) WALTER W. PALMER, *Governor*
> (Signed) LUTHER F. WARREN, *Regent*
> (Signed) JAMES ALEX. MILLER, *Regent*
> (Signed) ROBERT A. COOKE, *Regent.*"

Upon motion by Dr. James H. Means, seconded by Dr. Robert A. Cooke, and regularly carried, it was

Resolved, that members of the Board of Regents shall tender a Dinner to members of the Board of Governors at the St. Louis Session, as was done at the last Annual Session in Detroit.

President Bradley inquired if there was any desire to change the ruling with regard to any allowances for traveling expenses of the Regents for the Annual Sessions. There was a consensus of opinion that this should stand as at present, namely, their return convention and pullman fare, without any allowance whatsoever for hotel or other expenses.

Adjournment.

Attest: (signed) E. R. LOVELAND,
Executive Secretary

OBITUARIES

DR. HENRY S. PLUMMER

Dr. Henry S. Plummer was born in Hamilton, Minnesota, on March 3, 1874, the son of Dr. Albert Plummer and Isabelle Plummer. He died in Rochester, Minnesota, on December 31, 1936, of cerebral thrombosis. His early education was obtained in the local public schools and in the University of Minnesota. He attended the Medical School of Northwestern University, from which he received the degree of Doctor of Medicine in 1898. His first three years of practice were spent with his father in Racine, Minnesota, and in 1901 he entered The Mayo Clinic, where he continued the practice of medicine until his death.

In the early years of his practice he became deeply interested in roentgenology, bronchoscopy and esophagoscopy. His early work in the treatment of cardiospasm and esophageal stricture resulted in an important contribution to medicine, and his hydrostatic dilator and esophageal sounds, first designed and made by him in his own workshop, are still in use in the treatment of those conditions. Throughout his years of medical practice his greatest interest was in the function and diseases of the thyroid gland. Early in his experience, his keen clinical observations allowed him to define the two entities, exophthalmic goiter and hyperfunctioning adenomatous goiter. His development of a "two-product hypothesis" in exophthalmic goiter led, in 1921–22, to the demonstration of the beneficial effect of the administration of iodine to patients with exophthalmic goiter. This, his most outstanding contribution, has been responsible for a marked and general lowering in the mortality of exophthalmic goiter. His opinions on diseases of the thyroid are accepted as authoritative both in this country and abroad. His contributions to the literature were prepared with meticulous care, and were always the result of exhaustive study. He was apt, however, to leave unpublished a great deal that he knew and understood. It was this propensity that enabled him to teach his associates more by intimate contact and direction than by what he put into the literature.

Dr. Plummer's interests were, however, not limited to medicine. Whatever he became interested in he studied in the greatest detail. He gave much thought to the improvement of facilities for the care of patients, and the utilitarian features of the design of The Mayo Clinic building came largely from his mind. His opinions were sought on a variety of subjects, among them horticulture, building construction, and engineering.

Dr. Plummer was elected a Fellow of the American College of Physicians March 11, 1922, and served as a Regent of the College from 1923 to 1927. He was also a Fellow of the American Medical Association. He held membership in the Association of American Physicians, Association for the Study of Internal Secretions, American Association for the Advance-

ment of Science, American Association for the Study of Goiter, American Gastro-Enterological Association, Medical Library Association, American Association for Thoracic Surgery, American Public Health Association, Royal Society of Arts, Minnesota Pathological Society, Southern Minnesota Medical Association, Central Interurban Clinical Club, Minnesota Society of Internal Medicine, Central Society for Clinical Research, Minnesota State Medical Association, Olmsted-Houston-Fillmore-Dodge County Medical Society, Alumni Association of The Mayo Foundation, Sigma Xi, Alpha Omega Alpha, Minnesota Horticultural Society, University Club of Rochester, and St. Paul Athletic Club.

In 1920–21 he was the chairman of the Section on Practice of Medicine of the Scientific Assembly of the American Medical Association. In 1933 he was elected President of the American Association for the Study of Goiter, and in 1935 Northwestern University conferred on him the degree of D.Sc. (honoris causa). Since 1915 he had been Professor of Medicine, The Mayo Foundation, Graduate School, University of Minnesota.

Dr. Plummer was a keen observer and had a remarkable ability to correlate the masses of facts which he accumulated. He had great knowledge of human problems, and his philosophy of medicine was tempered by a wide humanitarian outlook. His sense of fairness was outstanding. In him were combined to a remarkable degree the finest characteristics of clinician and investigator. His life was devoted to a constant and unusually productive effort to improve the quality of the care of the sick. By his death Medicine has lost a prodigious worker and a great physician, and his associates have lost a friend, a guide, and an inspiration.

SAMUEL F. HAINES, M.D., F.A.C.P.

DR. JAMES ALLISON HODGES

JAMES ALLISON HODGES died on December 15, 1936, at the age of 78. Born in North Carolina, his early education was obtained at preparatory schools and at Davidson College in that State; in 1883 he was graduated from the department of medicine of the University of Virginia. After practicing several years in Fayetteville and Wilmington, N. C., he moved in 1893 to Richmond and became affiliated with the newly organized University College of Medicine as Professor of Anatomy. In 1896 he became Professor of Nervous and Mental Diseases and for a time served as President of that institution. Upon the merging of the University College of Medicine with the Medical College of Virginia in 1914 he became Professor of Clinical Neurology and Psychiatry in the latter, a position he held up to 1927, when he became Professor Emeritus. In addition to an extensive practice and teaching, he operated the Hygeia Hospital, a private institution, from 1903 to 1920, and for a number of years was medical director of a large life insurance company.

Dr. Hodges took an active and prominent part in a number of medical organizations. He was one of the founders in 1897 of the Tri-State Association of Virginia and the Carolinas, and in 1918 its President. In 1923 he served as President of the Richmond Academy of Medicine. In the Medical Society of Virginia he was always active, serving as President in 1930 and contributing regularly toward its welfare and advancement. In 1916 he became a Fellow of the infant American College of Physicians and might be considered one of its charter members.

A man of imposing presence, tremendous energy and great ability, Dr. Hodges was always ready to assist in any undertaking designed for the advancement of medicine or the betterment of society. A gifted speaker, his services were in much demand and numerous worthy causes profited from his efforts.

Following a coronary thrombosis a few years ago, Dr. Hodges' activities have been greatly restricted, but he continued up to the time of his death in full possession of his faculties and manifested a lively interest in contemporary affairs, both professional and civic.

J. Morrison Hutcheson, M.D., F.A.C.P.,
Governor for Virginia

DR. ERNEST E. LAUBAUGH

Dr. Ernest E. Laubaugh, Fellow and Governor of the American College of Physicians for the State of Idaho, died, December 13, 1936, after a four-day illness from influenza-pneumonia; at the age of forty-nine years.

Dr. Laubaugh was born at Shichshinny, Pennsylvania, August 20, 1887. He attended the public schools of Philadelphia and received his medical degree from the Medico-Chirurgical College of Philadelphia in 1909. He interned at the Mercy Hospital, Wilkes-Barre, Pennsylvania, 1909, and the Philadelphia General Hospital, 1910–11. He continued with this institution as Serologist during 1912–13. During 1911–12, he was Assistant Demonstrator in Physical Diagnosis, and during 1912–13, Assistant in the Department of Neurology of the Medico-Chirurgical College. In 1913, he accepted an appointment as Bacteriologist on the Idaho State Board of Health, which appointment he held until 1917. During 1919–20, he was Medical Advisor to the Department of Public Health of Idaho. From 1919–23, he was Consultant to the U. S. Veterans Hospital in Boise. At the time of his death he was a member of the staff of the St. Alphonsus and St. Luke's Hospitals in Boise.

During the World War, he was a first lieutenant in the U. S. Army, later advancing to a captaincy, and was stationed at the Port of Embarkation, Newport News, Virginia.

Dr. Laubaugh was a member of the Omega Upsilon Phi fraternity, Boise Physicians Club, Idaho State Medical Association, Southwestern Medical Society of Idaho, American Society of Bacteriologists, American

Heart Association; he was a Fellow of the American Medical Association, the American Society of Clinical Pathologists, and had been a Fellow of the American College of Physicians since 1927.

He made a number of contributions to medical literature and had held a distinctly outstanding position as an internist in Idaho and the northwest. He was a member of the Episcopal Church, American Legion and the Masonic fraternity. He is survived by his widow, Mrs. Beth Laubaugh; a son, James E. Laubaugh and a daughter, Lucile Laubaugh.

Those who knew him remember him as a quiet, genial, kindly and earnest physician, unassuming in manner, yet determined to keep abreast of the latest developments in his specialty and to give his patients always the benefits of his skill and care. Many Fellows of the College who took the official cruise to Cuba and Panama, following the last New Orleans Session of the College, will more vividly remember Dr. Laubaugh as one of the party. He had been a Governor of the College for the State of Idaho since 1928, and had served the College with the same efficiency, earnestness and integrity as he practiced his profession.

E. R. Loveland,
Executive Secretary

DR. WILLIAM FREDERICK WEGGE

William Frederick Wegge (Fellow), Milwaukee, Wisconsin, died on November 20, 1936, at the age of seventy-three.

Dr. Wegge, a native of Wisconsin, first studied dentistry at Baltimore University. After practicing that profession for a few years he returned to the University of Maryland School of Medicine, from which he was graduated in 1886. He took several post-graduate courses in Austria and Germany, specializing in mental disorders. Upon his return from Europe he did general practice for a short time and then held the position of Superintendent at the Northern Hospital for the Insane at Winnebago. Following his service at the State Hospital he located in Milwaukee, limiting his practice to neuropsychiatry. He was for many years Professor of Neuropsychiatry at the Milwaukee Medical College, and at the time of his death was Emeritus Director of the Division, and Professor of Clinical Neurology, Marquette University School of Medicine. He was a member of the Medical Society of Milwaukee County, the State Medical Society of Wisconsin, the American Medical Association, and Past-President of the Milwaukee Neuropsychiatric Society. He was elected a Fellow of the American College of Physicians in 1930.

Rock Sleyster, M.D., F.A.C.P.,
Governor for Wisconsin